CLINICAL SESSION • DENVER • DECEMBER 2 - 5, 1952

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THE JOURNAL

OF THE

American Medical Association

Volume 149, No. 15 — Published Weekly at 535 North Dearborn Street, Chicago 10, Illinois. Subscription, $15. Single Copy, 45 Cents — August 9, 1952

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Another appealing feature is the inclusion, under each drug, of information on the results of combining that drug with other drugs.

See SAUNDERS Advertisement on next two pages

SPECIMEN PAGE

We would like, of course, to take a pharmacologic whack at the anterior pituitary and make it stop its unreasoned behavior, but we do not know how to do this. So we have to use propylthiouracil, iodine and radioiodine for their repressive effects on the activity of the thyroid gland itself. Before considering the drugs individually I direct your attention to the comparison in general terms of the results achievable with the medical and surgical types of treatment (see Table 31).

Propylthiouracil

Source. This drug is prepared synthetically in the laboratory.

Clinical Effects. Estimates of the efficacy of the drug in thyrotoxicosis, granting the initial good effects in almost all cases, range from lasting benefit in one-third or fewer patients to similar results in as high as 85 per cent of instances. The probability of a sustained remission after discontinuance of propylthiouracil therapy appears to be greater in mild hyperthyroidism with a small goiter than in the patient with severe thyrotoxicosis and a large goiter. But I think those surgeons who are still claiming that the only place for the drug is to prepare the thyrotoxic patient for operation are possibly not seeing the whole truth. Admittedly, a disadvantage of propylthiouracil is that it does not remove the goiter and may indeed sometimes cause it to enlarge. But the recurrence rate after surgical treatment in the average hospital is probably almost as high as after medical treatment. Surgical mortality in hyperthyroidism is a very small fraction of 1 per cent in specialized clinics, but mortality in connection with the use of propylthiouracil is even less. And in general hospitals the surgical mortality is higher than that revealed by the published statistics of the specialized groups. Undoubted disadvantages of surgery are the cost of hospitalization and the surgeon's fees, the loss of time, the discomfort and the complications such as laryngeal paralysis, tetany and hypothyroidism. The recurrence rate after surgery in adenomatous cases is very low, and it should be granted that clear indications for surgery are the presence of solitary adenoma (there is a recognized tendency to malignancy), when there is otherwise a suspicion of malignancy, and when there is a large unsightly goiter, particularly if it is causing pressure symptoms. Otherwise, the pharmacologic therapy is the one of choice —say the internists!

Nature of Action. Propylthiouracil depresses the peroxidase enzyme system through which iodine is made available from the iodides in the thyroid gland. When the available thyroxin is used up the symptoms disappear, because no more thyroxin can be manufactured without iodine. However, the inhibitory effect on the anterior pituitary's production of thyrotrophic hormone is also removed when the thyroxin level falls, and the result is an increase in the hyperplasia, hypertrophy and vascularity of the thyroid gland. For a picture of frustration, see the thyroid gland under the influence of propylthiouracil!

Combination with Other Drugs. The combined use of propylthiouracil and iodine is routine practice in most clinics, particularly if the patient is being prepared for surgery (see Fig. 123). Iodine affects the thyrotoxic process in four ways: (1) it depresses thyrotrophic hormone activity, probably through action upon the hormone after it has reached the thyroid gland, and thus reduces the production of thyroxin from di-iodotyrosine; (2) it depresses the proteolytic enzyme that breaks down the large thyroglobulin molecule into smaller thyroxin molecules, thus "blocking" the liberation of thyroxin from the gland; (3) it appears to reverse the activity of the proteolytic enzyme that converts thyro-

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THE JOURNAL of the American Medical Association is published weekly by the American Medical Association. Subscription price, $15.00 a year, 45c a copy. Canadian $16.50. Foreign $19.00. Entered as second class matter June 25, 1885, at the Postoffice at Chicago, Ill., under act of March 3, 1879. Address all communications to American Medical Association, 535 N. Dearborn St., Chicago 10, Illinois

THE JOURNAL
of the American Medical Association
Published Under the Auspices of the Board of Trustees

VOL. 149, NO. 15 CHICAGO, ILLINOIS AUGUST 9, 1952
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DIAGNOSIS AND TREATMENT OF EPILEPTIC AND EPILEPTOID DISORDERS

Nicholas A. Bercel, M.D., Beverly Hills, Calif.

The subject of epilepsy is important in general practice since a little more than one out of every three private epileptic patients is treated by the general practitioner. The disease is as common as tuberculosis or diabetes. Although accurate descriptions of this disease have been available since biblical times, progress in diagnosis, let alone in treatment, began in reality only in 1870, when Jackson published his study on convulsions. The elusiveness of the diagnosis already plagued the ancient Romans, who were prompted to use tests by which attacks could be provoked artificially in slaves who were on sale. The difficulties of treatment were already known in the 19th century, when Esquirol put three epileptics in the hospital and tried one treatment after another, each different, on the same patient; every treatment was effective for a short time, but none brought about a lasting cure.[1] Even though a tremendous amount of progress has been made during the past 80 years, it seems that every new diagnostic device and every new anticonvulsant drug has added as many problems as it had solved.

DEFINITION AND INCIDENCE

"Convulsion" implies a motor element, which may be absent in most of the attacks; only 25% of seizures are generalized tonic-clonic motor fits, commonly called grand mal, while 71% consist of short-lasting disturbed states of consciousness, called petit mal, and only 3% of the attacks are described as psychomotor.[2] Epilepsy is a condition characterized by repetitious attacks. A single seizure, therefore, is not—although it may turn out to be—epilepsy. A good physiological definition of epilepsy is a tendency to "periodic involuntary neuronal explosions, most often resulting in either disturbed state of consciousness or motor release phenomena," [2] or various combinations in various degrees of both. Seizure is a term covering all forms of the epileptic attack and does not carry the prejudicious connotation that epilepsy does. Roseman's [3] definition, "a state of continuing dread interrupted by recurring attacks of involuntary behavior," ought to be preferable, being both realistic and comprehensive.

CAUSATION

In three out of four cases, the underlying cause is either unknown or unreliable; this kind of epilepsy is called idiopathic or essential. When the cause is known, one out of four, the condition is termed secondary or symptomatic epilepsy. Petit mal is more prevalent in infancy and childhood. Psychomotor epilepsy is most prevalent between the ages of 15 and 35. Grand mal, on the other hand, can occur at any time, at any age. The commonest idiopathic history consists of petit mal in the first five years of life, continuing with variable frequency up to adolescence, when it is replaced by or mixed with grand mal. In the majority of cases the epilepsy is idiopathic up to the age of 20. Tumors, infections (encephalitis and abscess), and hematoma are important causes between 20 and 40 years, whereas, after the age of 40, cardiorenal disease and cerebral vascular accidents will become increasingly frequent causes. Febrile convulsions are not uncommon between the ages of 1 and 3 years, and one out of five children with febrile convulsions will later become epileptic.

The over-all incidence of hereditary epilepsy is less than it is feared—a fraction of 10%. Lennox, Gibbs, and Gibbs, however, demonstrated about 60% abnormality in the brain wave records of blood relatives of epileptics, as contrasted with the 10% of the control group, who had no near relative with epilepsy. It is commonly thought that, however abnormal the brain wave record of an epileptic parent's child may be, if he did not have recurring convulsive attacks up to the age of 21, it is wholly unlikely that he will ever be afflicted with idiopathic epilepsy. The inheritance of abnormal brain waves might (but need not) be interpreted as a predisposition to epilepsy. The chances of a child's having epilepsy, if one parent is epileptic, is 1 out of 40, with a rising probability ratio when both parents are so af-

From the Department of Physiology, University of Southern California, Los Angeles, California.
Read at the Fifth Clinical Session of the American Medical Association, Los Angeles, Dec. 4, 1951.

1. Temkin, O.: Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology, Baltimore, Johns Hopkins Press, 1945.
2. Fetterman, J. L., and Weil, A. A.: Practical Aspects of Epilepsy (with Special Consideration of Epilepsy in Children), M. Clin. North America **31**: 1273-1288 (Sept.) 1947.
3. Roseman, E., and Aring, C. D.: Present Status of Epilepsy, California Med. **66**: 38-44 (Jan.) 1947.

flicted. These figures should be made available to those epileptics who so often want to put the decision of marriage and of having children up to the physician. While there may be a question about the advisability of marriage and family creation when both parties to the union are epileptic, counseling against it when only one partner is epileptic is more of a reflection on the insecurity of the adviser than a realistic appraisal of the facts as we know them today.

Birth injury, or birth anoxia, is probably a more important factor than is commonly realized. Nielsen [4] claimed that more than 50% of epileptics are first-born children, whose heads are subjected to the often traumatizing task of dilating the birth canal. Painstaking control of the anesthesia during delivery as well as better care of the newborn child and its respiratory problems could eliminate this unnecessary potential source of epilepsy.

Since the electroencephalogram can demonstrate central nervous system complications even in benign infections, such as infectious mononucleosis,[5] and since the same test done serially in a postacute period can point out focal potentially epileptogenic residuals, much of the guesswork surrounding the role of encephalitis can be done away with. Extension to the brain of the commonest childhood infections, especially scarlet fever, smallpox, influenza, measles, and typhoid, is fairly frequent. Sinus and middle ear infection used to supply a large percentage of abscesses, half of which predictably resulted in epilepsy. This is rapidly becoming a thing of the past, owing to the use of antibiotics.

Cerebral trauma, not counting subdural hematoma, is another important source. About 35% of dura-penetrating brain injuries—so common in war time—will result in post-traumatic epilepsy, while, in closed head injuries, the figure is much lower, none of the statistics going over 5%. Why so few patients with closed head injuries (which are very common) experience seizures might find an explanation in inherited cerebral dysrhythmia, which makes one more vulnerable to an accidental blow on the head. In brain trauma, serial electroencephalograms can monitor the clinically invisible state of events, pointing out the danger when post-traumatic seizure discharges make their appearance, which would even justify prophylactic anticonvulsant medication during the critical first two years following head injury, when the majority of post-traumatic epilepsies occur.

In any adult, when seizures supervene for the first time after the age of 20, cerebral neoplasm has to be looked for with bulldog tenacity. Two out of three tumors of the hemispheres result in seizures. Among the tumors most commonly causing seizures, seizure was the initial symptom in 68% of cases of astrocytoma, in 60% of meningioma, and in 51% of glioblastoma.[6]

4. Nielsen, J. M., and Butler, F. O.: Birth Primacy and Idiopathic Epilepsy, Bull. Los Angeles Neurol. Soc. **13**: 176-178 (Sept.) 1948.

5. Bercel, N. A.: Electro-Encephalogram in Cerebral Complications of Infectious Mononucleosis: Report of Case, J. Nerv. & Ment. Dis. **107**: 537-544 (June) 1948.

6. Hoefer, F. A. P.; Schlesinger, E. B., and Pennes, H. H.: Seizures in Patients with Brain Tumors, in Association for Research in Nervous and Mental Disease: Epilepsy, Baltimore, Williams & Wilkins Company, 1947, pp. 50-58.

7. Penfield, W., and Jasper, H.: Highest Level Seizures, in Association for Research in Nervous and Mental Disease: Epilepsy, Baltimore, Williams & Wilkins Company, 1947, pp. 252-271.

DESCRIPTION

The contributions of electroencephalography and neurosurgery (experimental neurophysiological studies on the human) have changed our thinking with respect to the various seizure types and their origin. Grand mal is often preceded by an aura that is part of the seizure and usually indicates that the epileptogenic focus is in the cerebral cortex. These auras either are patterned (indicating successive detonation of neighboring cortical areas), e. g., the Jacksonian march, or are focal seizures, which in turn might involve motor functions (of the eyes, head, limbs, and mastication) or sensory functions (somatic, visual, olfactory, and auditory sensations). Dizziness and a variety of psychical seizures associated with disturbed consciousness and automatic behavior may appear as the forerunner of an attack. Such seizures, if they occur without the generalized motor follow-up, are classified as minor or focal seizures. Petit mal is characterized by momentary loss of consciousness, although there may also be a few minor flickers of the eyelids, usually three per second, or jerks of the arms. These attacks rarely last longer than 30 seconds. It is customary to include in the petit mal triade the myoclonic jerk and the akinetic seizure consisting of loss of postural control. Seizures initiated by loss of consciousness, or consisting of loss of consciousness only, are referred to as highest level seizures. Penfield and Jasper [7] stated that

> . . . the opinion has been held traditionally that the highest level in central nervous system hierachy is to be found in the more recently acquired areas of the cortex, those areas which serve to distinguish the brain of men from that of the ape. Experimental and EEG data suggest that the frontal lobe is not the highest level, but that in the subcortex (particularly in some of the thalamic nuclei near the midline) there is a collection of nerve cells with ready access to all parts of the cerebral cortex which, when a neural discharge originates in them, will lead to instantaneous suspension of the conscious processes.

Psychomotor seizures are characterized by transient lapses of consciousness of different degrees accompanied by automatic behavior. They are often preceded by smacking of the lips, masticatory movements, and temporary arrest of speech. It is now believed that these seizures are focal in origin and that the focus is usually in or near the tip of the temporal lobe. Automatic behavior is a dangerous aspect of epilepsy, since, in this state, without the censorship and control of consciousness, the patient can engage in actions that may be violent and even homicidal. Many of such patients have been placed in state hospitals with false diagnoses, for which mistake there can be little excuse nowadays, since the electroencephalogram, particularly done while the patient is asleep, will pinpoint the characteristic psychomotor patterns and will make them available for medical or surgical treatment.

As the clinical and experimental material with respect to cortical localization accumulates, the baffling variety of conditions under which an epileptic attack can masquerade becomes more and more evident. The following conditions were found to be in reality minor epileptic attacks: paroxysmal abdominal pain, coronary occlusion, periodic mental dulness, anxiety hysteria, renal or biliary colic, acute appendicitis, Ménière's syndrome, syncope, paroxysmal perspiration, aphasia, blindness, migraine,

criminal psychopathic behavior, schizophrenia, manic-depressive psychosis, primary behavior disorder, hysterical fugue, enuresis, and nymphomania. One ought to be, therefore, sensitized to the fact that, whenever one deals with an attack that does not fit into the usual clinical picture, more particularly one that is refractory to proved accepted forms of treatment, its epileptic nature should be suspected and confirmed or ruled out by electroencephalographic study.

It is reliably estimated that 65% of children with behavior problems have abnormal records, as compared with a corresponding figure of 16% in a control group. The assumption is that there is similarity between the electroencephalographic pattern of the epileptics and of these children with behavior disorders, and that the symptoms of both groups are due to sudden periodic cerebral cortical changes.[8] The majority of these records show some form of paroxysmal dysrhythmia even though the true spike, or wave and spike, explosions of the classical epileptic are rarely encountered. Antiepileptic treatment, at times successful, has not reached a degree of reliability so that it could be used as a diagnostic counterproof. Since, however, periodic explosive behavior can be a form of epilepsy, the use of electroencephalograms in all cases of behavior disorders is justified, particularly when expensive long-term psychotherapeutic management or segregation in special classes is contemplated.

TREATMENT

Treatment of epilepsy—as of diabetes and tuberculosis—is a long-term program. Owing to the unpleasant and (to the uninitiated) frightening nature of an epileptic attack, the physician is often placed under a considerable amount of pressure on the part of the family or the patient to terminate the attack as soon as possible. This is not the primary aim of treatment, nor is it to use as few pills a day as possible. The general therapeutic principles can be expressed in the following way:

1. Finding the most suitable anticonvulsant and its right dose requires an average of six months. 2. One should start out with the best established drug that has proved its value and increase the dose slowly, in order to avoid the toxic effects that are common at the beginning of treatment with a new medicament or when the dose is increased suddenly. 3. One should change to newer medications only when the older ones used in adequate near-toxic doses have consistently failed. The more recent a drug, the more toxic it is, which means that precautionary laboratory examinations will also make them more expensive. 4. One should not follow fixed formulas; anticonvulsant medication has to be tailor-made. 5. Epileptics do not live on drugs alone. With these principles in mind, approximately 70% of all epileptics who have seizures can be successfully controlled or the seizure incidence decreased to the minimum.

Bromide.—This drug, introduced in 1853, was the first successful anticonvulsant. It is used chiefly in institutionalized epileptics. It appears that the side-effects of bromide medication have been exaggerated and the virtues neglected. The therapeutic dose is 5 to 15 grains (0.30 to 1 gm.) of the sodium or the triple salt, given two or three times a day.

Phenobarbital Sodium.—Phenobarbital sodium, introduced in 1912, still one of the best standbys, is quickly effective if taken on an empty stomach; on the other hand, the action lasts longer if it is taken after meals. The average dose is 1½ grains (0.10 gm.), taken three times a day, a single dose giving protection for approximately 6 to 12 hours. The commonest cause of status epilepticus (continuous seizures) is sudden cessation of phenobarbital medication. Bromides and phenobarbital sodium have a sedative effect, which varies from patient to patient.

Diphenylhydantoin Sodium.—A great landmark in modern treatment of epilepsy was the introduction of the use of diphenylhydantoin (dilantin®) sodium by Merritt and Putnam, in 1938. This drug (either the sodium salt or in oil), considering its low toxicity and high efficacy, is the best available anticonvulsant. It should be given after meals, with a single capsule of 1½ grains at the start and the dose increased by one capsule every week, until either signs of toxicity appear or seizures are controlled. By the time six capsules, in equally divided doses, are given a day, if seizures continue, one should consider combining this treatment with the administration of 1½ grains of phenobarbital sodium, particularly at nighttime, rather than increase the dose. Gradual increase until the effective dose is reached is the best safeguard against the toxic reactions, consisting of ataxia (some patients have been arrested for drunkenness), drowsiness, blurring of vision, morbilliform rash, gastric distress, and hirsutism. Hypertrophy of the gums occurs more often; massaging with rubber tooth brushes, strict dental care, and occasional surgical removal of the protruding excess gum is advisable. Because of the slow decomposition of the drug in the system, it can also be given in the morning, all at once.

Trimethadione.—The drugs so far mentioned have comparatively little effect on the petit mal triad. In fact, in some patients these minor seizures might be aggravated by the administration of diphenylhydantoin alone. The introduction of the use of trimethadione (tridione®), by Lennox, Richards, and Perlstein, constitutes an advance in treatment for petit mal no less outstanding than the discovery of diphenyldantoin for use in grand mal. The dose should be one capsule of 5 grains (0.30 gm.) for infants, two capsules between the ages of 2 and 4, and three capsules from 5 years and upward. These amounts may be increased to a maximum of three times the above amounts. Among the toxic by-effects are sensitivity to light, particularly at the beginning, and drowsiness. Trimethadione is a potentially dangerous drug, because it depresses the hematopoietic system, and some fatalities from resultant agranulocytosis and pancytopenia are on record. These occurred as often at the beginning of as after prolonged medication. Gradual administration is again the rule. A biweekly and, later (after two months), a monthly complete blood cell count, including a platelet count, is a necessity. Should the neutrophil count, which often indicates an insignif-

8. Kennard, A. M., and Willner, M. D.: Significance of Paroxysmal Patterns in EEG'S of Children Without Clinical Epilepsy, in Association for Research in Nervous and Mental Disease: Epilepsy, Baltimore, Williams & Wilkins Company, 1947, pp. 308-328.

icant drop, reach 2,500, decrease in dosage or even temporary discontinuance of medication is advisable. Unfortunately, even blood cell count monitoring may not give a sufficient warning, because of the insidious nature of neutropenia, for which reason this drug should not be given to patients who have a history of allergic hypersensitivity to other drugs. It seems that trimethadione given alone will aggravate grand mal seizures. In patients with mixed seizures, therefore, it is well to combine trimethadione with either phenobarbital sodium or diphenylhydantoin sodium.

Paramethadione.—For those who are refractory to trimethadione medication, an allied preparation called paramethadione (paradione®), given in similar doses might be of value, it being clearly understood that the same precautionary measures must be observed. Paramethadione therapy is effective in cases of "highest level" seizures. Approximately 80% of patients with petit mal will show a good response to medication with the "diones."

Methylphenylethyl Hydantoin. — Methylphenylethyl hydantoin ("mesantoin") has been recently introduced and found to be efficacious in patients who fail to respond to diphenylhydantoin sodium therapy. The mode of administration and the dose are those identical with the latter drug, but, because of its relatively greater toxicity, special emphasis should be placed on slow, gradual increase to the effective dose, e. g., one-half tablet per week. Sleepiness is a common side-effect, while lymphadenopathy, morbilliform rash, exfoliative dermatitis, and neutropenia have occasionally occurred. A few cases of fatal blood dyscrasia have also been reported. As with diphenyldantoin sodium, it is best to add phenobarbital sodium if six tablets of methylphenylethyl hydantoin per day fail to produce the desired effect. Experience indicates its efficacy particularly in cases of grand mal and Jacksonian convulsions, with less effect in cases of other forms of seizures.

Phethenylate Sodium and Phenacemide.—Phethenylate ("thiantoin") sodium and phenacemide (phenurone®), two newer drugs, are also available. The latter is especially effective for psychomotor attacks, but, besides blood cell counts, liver function tests are a necessity for the detection of liver damage, which occasionally occurs.

Other Forms of Treatment.—In status epilepticus, slow intravenous injection of phenobarbital sodium, amobarbital sodium, vinbarbital ("delvinal") sodium, paraldehyde, and trimethadione is of definite value. Diphenylhydantoin sodium can also be given, through a stomach tube, along with fluids, electrolytes, and nutrients. In the refractory cases, sometimes heroic measures are needed; one has to diverge from the beaten track. Thus the use of amphetamine sulfate often helps in petit mal cases, as does the introduction of gas in the subarachnoid space by means of ordinary pneumoencephalography. Electric convulsive treatments—which raise the convulsive threshold after each seizure—were used not only with impunity but with success when everything else failed. Carbon dioxide inhalation has also been tried and has been of value. Putnam and co-workers [9] advocated "hyperintensive" treatment either with continued barbital narcosis or with toxic doses of the whole battery of anticonvulsants given on successive days; the physician should then choose the combination of drugs as a steady regimen that most improves the electroencephalogram.[9] Some drugs given in toxic doses, paradoxically, increase the electroencephalographic seizure pattern; their use should be abandoned altogether. The underlying philosophy of these special measures is the same: one's ingenuity should never concede defeat to epilepsy.

Because of technical difficulties, ketogenic diet and the administration of glutamic acid are not in great favor. Food substances producing alkalosis should be decreased and replaced by a diet that produces acidosis. The use of alcoholic beverages in any amount is absolutely contraindicated in successful treatment of epilepsy.

Surgical treatment (consisting of removal of posttraumatic scars and subpial resection of atrophied gyri) has been advocated in cases in which medical management, after a conscientious trial, has failed. In cases of refractory psychomotor epilepsy, good results may be obtained with the recently developed temporal lobectomy, which is not as yet universally adopted, although preliminary reports show encouraging results.[10] According to these, unilateral electroencephalographic spike focus, organic pathological changes, absence of rage, and good interseizure personality are related to the best postoperative results.[11]

Poor cerebral circulation due to inadequate blood flow and oxygenation is receiving increasing attention. Breathing exercises as well as any form of physical exercise are to be encouraged, even though some patients are sensitive to the results of overventilation. If they can be taught to control their breathing and therefore keep carbon dioxide from being dissipated, the nonviolent sports are permissible. Improvement of general circulation and accumulation of lactic acid with exercise are the advantages that far outweigh the small statistical probability of bringing about a seizure owing to overbreathing. Although the exact mechanism is not known, emotional upset and sudden discharges of intense affect at times will initiate an attack in the epileptic.

COMMENT

While statistics indicate that only 18% of colleges in the United States refuse admittance to epileptics,[12] only 48 per 1,000 epileptics attend college. If this is due to unofficial discrimination, this cannot find justification in the assumption that epileptics as a group have a lower I. Q., because, as a matter of fact, 65% of them have above average intelligence.

While epileptics should not be encouraged to engage in occupations where they are exposed to danger by machines, the blanket refusal of occupation in factories and stores is not justified. The personnel offices of most large firms submit a questionnaire in which the occur-

9. Putnam, T. J.; Bercel, N. A., and Rothenberg, S.: Hyperintensive Treatment of Recalcitrant Epileptics, to be published.

10. Bailey, P., and Gibbs, F. A.: Surgical Treatment of Psychomotor Epilepsy, J. A. M. A. **145**: 365-370 (Feb. 10) 1951.

11. Green, J. R.; Duisberg, R. E. H., and McGrath, W. B.: Focal Epilepsy of Psychomotor Type, J. Neurosurg. **8**: 157-172 (March) 1951.

12. Potter, G.; McBride, M., and Lennox, W. G.: Distribution of Medical Care and Higher Education of Epileptics, in Association for Research in Nervous and Mental Disease: Epilepsy, Baltimore, Williams & Wilkins Company, 1947, pp. 539-560.

rence of epileptic seizures is prominently displayed. At present, many an epileptic has to perjure himself and run the risk of refusal of compensation in case of accident if he wants to make a living.

In certain states, such as California and New Jersey, it is mandatory that the physician notify the authorities whenever he handles an epileptic. There is no statistical evidence indicating that a larger percentage of epileptics are subject to traffic accidents than are normal persons. While it is good practice to prohibit driving, exceptions should be made in the cases of well-controlled, nondrinking, conscientious, and intelligent patients, and such factors as sufficient warning, strictly nocturnal attacks, and rare seizures should receive proper consideration. In some states, the personnel of the motor vehicle department judge every case on its own merit, with ample advice from and cooperation with the treating physician. A partial solution to this problem might be the issuance of temporary driver's licenses, renewable every three or six months, after recheck by the treating physician. One would welcome a comparable zeal on the part of authorities if they were to clear the highways of recidivant alcoholic drivers, a far greater potential source of accidents.

Friendly, trustworthy cooperation between physician and patient is of great importance in cases of epilepsy. The International League Against Epilepsy is an effective alliance among physicians, patients, and lay groups, which is exerting an unceasing effort to better the unenviable lot of the epileptic. Every physician should encourage his patient to join the league and use his influence to promote this remarkable enterprise.

It cannot be hoped that the lot of the epileptic can be successfully improved until every physician, particularly the general practitioner, undertakes an educational role in his community in order to change prevailing public attitudes. The following statistics are from a recent public opinion survey [13] on a national scale: 50% of persons interviewed had actually witnessed a seizure; school and play participation by epileptics was approved by over half and objected to by one-quarter; employment was advocated by 45% and objected to by 35%. While this reflects a significant progress in the understanding and acceptance of persons subjected to convulsive disorders, there still prevails enough ignorance about the epileptic, particularly in small communities, to amount to a dark stigma, which is just as undeserved as it is unjustified. The aim of treatment in epilepsy, therefore, is not just control of the seizures but also assistance to the epileptic in his adjustment on a social and economical as well as educational level.

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CLINICAL-ELECTROENCEPHALOGRAPHIC CORRELATIONS, WITH SPECIAL REFERENCE TO EPILEPSY

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Although correlations of a high degree of statistical significance have been demonstrated between changes in the electroencephalogram and certain clinical conditions, notably in epilepsy and focal organic brain lesions, every electroencephalographer is aware that dissociation of the electroencephalographic pattern and the clinical status is not uncommon. To the investigator, these facts are of great importance, since they suggest clues regarding the functional significance of rhythmical cortical electrical activity. From the clinician's standpoint, however, such discrepancies are disappointing; for, in spite of logical reasons to the contrary,[1] the hope is still widespread that a laboratory test will someday be found that will furnish clinical diagnoses. Experience with electroencephalography has shown that this is not the case, but the view is still prevalent that with the aid of the electroencephalogram one can distinguish between "functional" (usually meaning psychogenic) and "organic" (usually meaning nonpsychogenic) states.

It is the purpose of this paper to call attention to evidence that clinical and electroencephalographic changes may be widely dissociated and to discuss the significance of these findings with regard to the possible functions of spontaneous cortical electrical activity and the use of electroencephalography in clinical practice. Much of the clinical evidence is well known to electroencephalographers. However, additional illustrative material will be drawn from incidental observations on clinical-electroencephalographic studies that have been made in the course of investigations of other problems.[2] The term electroencephalogram, as used in this paper, refers to the spontaneous electrical activity of the brain as recorded clinically from scalp and, in some cases, basal leads in man, and from implanted dural leads in animals, under standard conditions.

PSYCHOSES

It is well known that the electroencephalograms of most patients with schizophrenia are within normal limits. Whether this syndrome is always associated with "cortical dysfunction" may be debatable, but there can be little doubt that impairment of cortical function is associated with both mental deficiency and Korsakoff's psychosis. Yet, in the former, entirely normal electroencephalograms are often encountered, and such dissociations have also been observed in the latter condition.[3]

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Read at the Meeting of the American Psychiatric Association, Cincinnati, May 10, 1951.

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Normal electroencephalograms may also be recorded in patients with cortical atrophy demonstrated pneumoencephalographically.[4] Toxic deliriums of various sorts are usually associated with abnormalities in the electroencephalogram. However, Romano and Engel [4] found that such changes are correlated with disturbance of consciousness and not with "character and expression of anxiety, the content of thought, and the nature of sense deceptions," even though the changes may be presumed to be associated with cortical dysfunction. Furthermore, in deliriums of long standing, the electroencephalogram tends to return to a more normal pattern.[5]

Occasionally during chronic barbiturate intoxication, and very frequently during the barbiturate abstinence syndrome that follows abrupt withdrawal of the drug, psychoses may be observed. It is of interest that these "toxic" psychoses may assume the form of almost any psychiatric nosologic entity in different persons and in the same person at different times. Anxiety and panic states and hallucinatory-delusional, confusional, delirious, or amnesic-confabulatory syndromes have been observed. The concomitant electroencephalographic patterns are variable, and in some instances they may be within statistically normal limits, even when the patient is extremely disturbed. When the patient has apparently recovered completely by clinical standards, the electroencephalogram may be within normal limits and yet gross evidence of "organic" brain dysfunction may be revealed by the Rorschach technique. While impairment of consciousness is usually associated with electroencephalographic changes in the barbiturate addiction cycle, the relationship is not quantitative. This may be demonstrated most strikingly in nonpsychotic subjects during chronic barbiturate intoxication.[2] The relationship between states of consciousness and electroencephalographic changes will be further discussed below.

AFFECTIVE STATES

Many of the psychotic states referred to above are associated with disturbances of affect, and, as has already been noted, they do not appear to be related quantitatively to changes in the electroencephalogram. Such dissociation can also be demonstrated by the administration of certain drugs to nonpsychotic persons. In patients with previous histories of drug addiction ("post-addicts"), the intravenous injection of as much as 30 mg. of morphine almost invariably produces pronounced euphoria, accompanied by a transient "thrill" a second or two immediately after injection, which the subjects compare with orgasm. Concomitantly, in the majority of subjects, no significant changes can be detected by inspection in electroencephalographic tracings from multiple scalp and basal leads.[2] In the same subjects, dysphoria may be induced by large doses of mescaline or N-allylnormorphine.[6] When the affective experience is pronounced, there may be a reduction in the percentage time that alpha activity is present in the record ("alpha percentage") and also in the average voltage of alpha activity. The strong affective state may not be unpleasant. Some post-addicts whose electroencephalograms showed such changes described their experience as one of "drive"; others, as one of "anxiety." Apparently the electroencephalographic changes are related not to the quality of the affective experience but to the degree of "arousal" with which it is associated.

CHANGES IN CONSCIOUSNESS

While sleep and stupor are always associated with fairly characteristic electroencephalographic changes, the latter may be encountered occasionally in persons who are wide awake, as judged by their responsiveness to whispered instruction or by their continual execution of regular voluntary activity during recording (for example, rhythmical finger tapping).[2] Dissociated electroencephalograms of this sort have been recorded with epileptic patients during seizure-free intervals and include patterns characterized by alternating rhythmical "spindles" and slow waves, or continuous 2 to 4 cps delta activity. Continuous delta activity may also dominate in the records of patients who have been treated by repeated electroshock convulsions but who were certainly not stuporous at the time the electroencephalogram was made, several days after the last treatment. During chronic addiction to methadone, patients may have electroencephalograms that consist largely of continuous 5 cps rhythmic activity, even though a pronounced tolerance has clinically developed in the subjects and they are awake throughout the period of recording.[7] Likewise, during chronic barbiturate intoxication, there is no quantitative relationship between the severity of the electroencephalographic changes and the degree of impaired consciousness. Indeed, the electroenchephalograms of the subjects who are quite wide awake may be indistinguishable from those of nontolerant subjects who have been anesthetized by intravenous injection of barbiturates.[2]

Striking dissociations of electroencephalographic "sleep patterns" and states of consciousness have also been demonstrated in animals. In the rat, moderate doses of morphine (20 mg. per kilogram of body weight subcutaneously) produced alternating fast "bursts" and slow rhythms that resembled closely those produced by pentobarbital (30 mg. per kilogram intraperitoneally). Yet, after the doses of morphine, the rat was certainly not asleep, since it had to be restrained in a holder to permit recording, while after the injection of the doses of barbiturates, the animal was anesthetized.[8]

Similar findings have been observed in the dog. In this species, a subcutaneous injection of 5 mg. per kilogram of morphine produces regular, long-recurring "bursts" and slow wave patterns, chiefly bifrontal, which disappear abruptly when the dog is called or whistled to. In contrast, similar electroencephalographic changes that are produced by intravenous injection of 13 mg. per kilogram of pentobarbital are not altered at all by these or other more intense stimuli. After the subcutaneous injec-

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tion of convulsive doses (40 to 60 mg. per kilogram) of methadone in dogs, three successive types of change may be noted in the electroencephalogram: (*a*) a "burst and slow wave" pattern, (*b*) a continuous low to moderate voltage fast activity superimposed on low voltage slower rhythms, with occasional high voltage random spikes, and, finally, (*c*) recurring, rhythmic, high voltage spike discharges. Early during stage (*b*) the dog may respond readily to stimuli, but, later, the animal may be entirely unresponsive. Very striking dissociations of electroencephalographic "sleep patterns" and behavior may also be demonstrated in dogs after the administration of N-allylnormorphine (2.5 mg. per kilogram) or of atropine (5 mg. per kilogram). Although the electroencephalogram is dominated by the "burst and slow wave" pattern, the dog may be restless and a restraint may be required to permit recording.

Converse dissociations have also been demonstrated. Magoun [9] reported that "In . . . animals with large hypothalamic and midbrain tegmental lesions, the excellence of electroencephalographic activation induced by afferent stimulation contrasted sharply with the poverty of associated behavorial arousal and the lesions appeared, in fact, to have dissociated the two features of the waking state."

SENSORIMOTOR ALTERATIONS

It is well known that sensory stimuli may be followed by an abrupt cessation of the alpha rhythm. In man, light stimuli are most effective. However, there is evidence that such stimuli produce their effects on the electroencephalogram not because of the specific anatomic arrangement of the visual system but because of the attention that they arouse.[10] Vivid visual hallucinations may be induced regularly in man by oral administration of about 5 mg. per kilogram of mescaline. Concomitantly, the alpha percentage may or may not be reduced. Usually, the subject's reports of visual hallucinations coincide with a transient reduction in alpha activity, but the sensory experiences may also occur in the absence of concomitant changes in the electroencephalogram. Conversely, marked changes in electroencephalographic tracings from the occipital regions may be noted in persons whose sensory visual system is unimpaired. Thus, in children with intact vision, subtentorial tumors may be responsible for "focal" delta activity in one or both occipital lobes, presumably because of upward pressure on the easily displaced tentorium.[2]

Jasper and Andrews [11] found that a close relationship could be demonstrated between the frequencies of the alpha rhythm recorded from the motor areas and the frequencies of finger tremors and that light stimuli produced parallel changes in both. However, these observers also noted exceptions in which electroencephalographic and finger tremor frequencies could be dissociated. One may observe clinically, in patients with various cerebral neurological disorders, the occurrence of maximal electroencephalographic changes in tracings recorded from locations on the scalp that are relatively remote from the presumed site of the organic lesion. Often, in these cases, no dysfunction can be demonstrated that can be related to the cortical area corresponding to the location of maximal electroencephalographic changes.[2] Further examples of the dissociation of electroencephalographic patterns and motor activity will be discussed in relation to epilepsy.

EPILEPSY

"Paroxysmal activity," or suddenly appearing high voltage fast or slow rhythms, is indeed highly correlated with epilepsy. The nature of the seizures exhibited by the epileptic patient is more closely related, however, to the locus of origin of the paroxysmal electroencephalographic discharge than to the patterns of the discharge.[12] Furthermore, there is a considerable body of evidence indicating that the "epilepsy," in the clinical sense, is determined not only by the presence of paroxysmal activity in the electroencephalogram but by the coexistence of other factors as yet unknown.

In patients with organic brain damage, as in severe post-traumatic states, or with brain tumors, focal paroxysmal abnormalities may exist in the absence of fits of any kind. In the nonepileptic post-addicts, hydration caused by vasopressin injection (pitressin®) may produce paroxysmal alterations in the electroencephalogram without seizures of any sort.[13] During the barbiturate abstinence syndrome, a severe paroxysmal mixed spike and slow wave activity may be observed in the electroencephalogram, with or without concomitant clinical seizures. Likewise, in some patients with epilepsy, severe paroxysmal disturbances may continue unabated, while overt seizures may be prevented entirely by administration of diphenylhydantoin (dilantin®) sodium. In patients with petit mal epilepsy, Jasper and Andrews [11] found that by overbreathing, ". . . one to ten of the spike and slow wave patterns would appear before clonic movements could be detected." Similar dissociations can be demonstrated in dogs after administration of convulsive doses of pentylenetetrazole (metrazol®). White and Giarman [14] have shown that in dogs anesthetized with cyclopropane, the intravenous injection of procaine may evoke long-sustained, continuous, diffuse high voltage "spike and dome" rhythms in the electroencephalogram, without any concomitant motor changes.

Dissociation of electroencephalographic patterns and clinical manifestations has also been observed in recent studies on the relation of the anterior portion of the temporal lobe to psychomotor epilepsy. While Gibbs, Gibbs, and Fuster [15] found that clinical evidence of psychomotor seizures was present in the great majority of epileptics in whom spike foci could be demonstrated in the anterior temporal lobes, this was true in only 46% of similar pa-

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tients who were studied by Jasper, Pertuisset, and Flanigin.[16] In the latter series, a marked improvement after resection of the anterior temporal lobe was usually associated with the disappearances of the electroencephalographic foci, but exceptions were also noted. Conversely, subjective disturbances in patients with temporal lobe disease may be aggravated, while generalized seizures are controlled by anticonvulsant therapy.[17]

COMMENT

That clinical-electroencephalographic dissociations may be demonstrated should not be surprising, for "correlations" between two sets of data imply only the possible existence of common mechanisms. "Clinical" entities are defined arbitrarily from a utilitarian standpoint, and classifications of disorders may be revised if, by so doing, prediction or treatment is furthered. "Laboratory" data are expressed in the framework of hypothetical constructs that are implicit in the use of particular techniques; and, therefore, the functions they measure may contribute to, but rarely, if ever, determine, the clinical phenomenon under investigation. Therefore, the cause, and even the definition, of clinical entities is nearly always "multifactorial." In the case of epilepsy, the demonstration of "paroxysmal activity" in the electroencephalogram does not alone define the clinical condition. Other factors, perhaps pathologically lowered thresholds of neurons that may be depolarized by electrical field changes induced by "paroxysmal" voltage disturbances arising from independent sources, may be required for the production of epilepsy in the clinical sense. It follows, therefore, that clinical terminology should not be used to describe laboratory data. Cogent reasons have been adduced for avoidance of the terms petit mal, grand mal, and psychomotor in describing electroencephalographic patterns.[18] One may go further and suggest that the word epileptic be avoided also in describing high voltage paroxysmal discharges.

Several alternative hypotheses may be advanced to explain the clinical-electroencephalographic dissociations that have been described. However, for clinical orientation and for use in further research, it may reasonably be inferred that the alpha and beta rhythms, and the diffuse changes that may occur in the electroencephalogram in the direction of synchronization or desynchronization, are determined by activity in a specific neuronal system that is, at least in part, independent of those subserving such cerebral functions as ideation, mood, consciousness, and possibly sensory and motor activity. Such a view is compatible with known facts concerning the neurophysiological basis of the electroencephalogram and the effects of drugs thereon.[19]

The functions of such a hypothesized specific neuronal system have yet to be elucidated. That it may subserve a "scanning" mechanism concerned with sensory perception and attention has been suggested by McCulloch[20] and Walter.[21] Evidence that it may subserve homeostatic functions has been adduced by Jasper[10] and Magoun.[22] However, alternative interpretations are possible concerning the specific conditions under which such homeostatic responses are likely to occur.[23]

Such hypotheses have opened new fields for investigation that may clarify greatly the proper use of the electroencephalogram in clinical practice. At present it appears timely to stress the importance of avoiding clinical terminology in describing electroencephalographic changes and to emphasize the "multifactorial" nature of clinical entities.

SUMMARY

Clinical, physiological, and pharmacologic evidence is presented indicating that wide dissociations may occur between electroencephalographic patterns and changes in sensorium, the state of consciousness, sensation, motor activity, and ideation. It is postulated that the alpha and beta rhythms, and the diffuse changes that may occur in the electroencephalogram in the direction of synchronization or desynchronization, are determined by a specific neuronal system that is, at least in part, independent of neuronal systems that subserve behavior. Hence, changes in the electroencephalogram, particularly those that are diffuse and bilaterally synchronous, can represent only one factor that contributes to the genesis of any clinical entity, including epilepsy.

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Brucellosis of the Urinary Tract.—Brucellosis of the urinary tract should be suspected in all patients complaining of urinary symptoms whose past history reveals previous systemic infection due to Brucella. Acute cystitis and roentgenographic evidences of pyelonephritis with deposits of calcium are suggestive signs. The presence of pyuria in the absence of bacteria when routine staining and cultural methods are employed lends further suggestive evidence. Positive blood agglutination reactions for Brucella at high titers, for example, 1:400, provide corroborative evidence. It must be remembered that brucellergin skin testing and a "therapeutic trial" of Brucella vaccine therapy may greatly increase the agglutinins; the agglutination reaction has uncertain diagnostic value if performed after either of these procedures. A definitive diagnosis is established by isolation of the Brucella organisms on suitable media.

Therapy with a combination of dihydrostreptomycin and sulfadiazine in our cases produced prompt and gratifying relief of the patients' symptoms. . . . A newer and more successful method of treating brucellosis has recently been advanced. This consists of the daily administration of 750 mg. of aureomycin every six hours together with 1 gm. of dihydrostreptomycin every 12 hours. Such therapy is continued for 12 to 14 days in cases of acute brucellosis and for 21 to 28 days in cases of chronic or complicated disease. This combination of drugs appears to be superior to the combination which we employed. —Laurence F. Greene, M.D.; Lyle A. Weed, M.D., and Donald D. Albers, M.D., Brucellosis of the Urinary Tract, *The Journal of Urology*, May, 1952.

TREATMENT OF MALARIA WITH A SINGLE DOSE OF AMODIAQUINE OR CHLOROQUINE

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Since the development of 4-aminoquinoline compounds, particularly chloroquine (aralen® [Winthrop-Stearns]) and amodiaquine (camoquin® [Parke-Davis]), the treatment of malaria has become much simpler than it was a few years ago. Published reports stress the rapidity with which symptoms are alleviated and the speed with which parasites disappear from the peripheral blood when either of these drugs is administered.

Chloroquine and amodiaquine have the following pharmacologic and clinical properties in common: 1. They are rapidly and essentially completely absorbed from the gastrointestinal tract of experimental animals and presumably of man. 2. They are distributed unequally in the body tissues and are present in much higher concentrations in some tissues than in blood plasma. 3. They are slowly excreted from the body on cessation of drug therapy. 4. They are highly effective in terminating acute attacks of malaria due to either Plasmodium falciparum or P. vivax. 5. They usually result in complete eradication of P. falciparum infections. 6. They decrease the number and frequency of P. vivax relapses. 7. Neither has any marked gametocidal effect. 8. Neither has any marked effect against sporozoites, and therefore both are without prophylactic value. 9. Toxic effects with therapeutic doses are insignificant.

Chloroquine is 7-chloro-4-(4-diethylamino-1-methylbutyl-amino)-quinoline. In the World War II evaluation of potential antimalarials, it emerged as one of the more active and least toxic quinoline derivatives. Consequently it was employed widely, and has given satisfactory results in thousands of infections. It is commonly supplied in the form of the diphosphate as 250 mg. tablets, of which 150 mg. (or 60%) are chloroquine base. The usually recommended treatment of acute malaria in nonimmune persons consists of administration of 4 tablets (1 gm.) as an initial dose, followed by 2 tablets (500 mg.) after 6 to 8 hours and 2 tablets on each of two successive days.

Amodiaquine is 4(3′diethylaminomethyl-4′hydroxyanilino)-7-chloroquinoline, supplied in the form of dihydrochloride dihydrate. It was synthesized in 1946, and subsequent trials in several parts of the world have demonstrated good results with doses frequently even smaller than those recommended for chloroquine. The 300 mg. tablets contain 200 mg. of the base. Three tablets equal 0.6 gm. of the base, and 2 tablets 0.4 gm.

From the time of its first clinical trials, amodiaquine has been frequently employed as a single dose treatment and as a one day treatment. This is true also for chloroquine, but most clinicians have prēferred the three day regimen referred to above. To date, there seems not to have been any large scale study that directly compares the therapeutic effects of these two compounds, gram for gram.

In our hands [1] 0.6 gm. of amodiaquine base in a single oral dose has been completely satisfactory for treatment of acute attacks of both P. falciparum and P. vivax malaria in northwestern Honduras. We wondered whether chloroquine might be as effective when given in a comparable single dose in the same geographic area. One previous publication [2] provided a clue. Butts reported a series of 449 cases of malaria in Honduras, Costa Rica, and Panama, in which treatment with chloroquine was given on 16 schedules; 92 of this group received single doses of the drug varying from 0.08 gm. of base to 0.62 gm. of base. Butts noted that these amounts of chloroquine "appeared almost as satisfactory in this adult immune group as large doses extended over a three day period." We thought it worth while to explore further the practicability of single dose treatment with chloroquine or amodiaquine on a comparative basis.

MATERIAL AND METHODS

This study is based on the treatment of 600 persons who resided in or near the Tela Railroad Company (United Fruit Company) headquarters at La Lima in northwestern Honduras. This is an area where Anopheles albimanus is the principal vector and where malaria is endemic all year around, but of slightly decreased incidence during the dry season from May to September. Because of the endemicity of the disease, the adult native population may be considered as a relatively immune group. All of these patients were hospitalized between February, 1950, and May, 1951, in the Tela Railroad Company Hospital located in La Lima.

The ages ranged from 7 years to 61 years. Eighty-six per cent were males and 14% were females, the difference being explained by the fact that the experiment was conducted largely on the male medical wards of the hospital. All were of mestizo stock, and represented various mixtures of Indian, Negro, and Spanish ancestry.

Amodiaquine was given to 380 patients, including 325 of the previously reported group.[1] They were placed in one of four groups to which either 0.4 gm., 0.6 gm., 0.8 gm., or 1.0 gm. of the base was given in a single dose. Chloroquine was given to 220 patients. As a result of experience already gained in the amodiaquine series, only two chloroquine schedules were employed: 0.45 gm. of base (0.75 gm. of aralen®) or 0.6 gm. of base (1.0 gm. of aralen®) given in a single dose.

Whichever of the two compounds was employed, the amount of drug and the time of administration were not related to the parasite density, to the stage of the parasite cycle observed in the blood film, or to the degree of fever. As soon as a diagnosis was confirmed by blood film, the patient was treated with whichever schedule was currently in use. Amodiaquine treatment was given from February, 1950, through December, 1950. Chloroquine treatment was given from January through May, 1951. The oral temperature was recorded every four hours on all patients. Throughout the hospitalization, thick blood films were examined twice daily, at 6 a. m. and at 3 p. m. The groups were comparable in respect to degree of parasitemia when treatment was started.

RESULTS

Clinical Response.—By reference to the table, it can be seen that only the 0.45 gm. dose of chloroquine did not prove to be quite satisfactory. There is indication that

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Dr. A. J. Walker of Tulane University of Louisiana assisted in preparation of this manuscript.

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patients with P. falciparum malaria treated with 1.0 gm. of amodiaquine base achieved a normal temperature a little more quickly than persons given lesser amounts of this drug, but a similar difference is not noted in the temperature response of patients with P. vivax malaria. In all but nine patients headache, malaise, vomiting, joint pains, and other symptoms attributable to malaria disappeared within 36 to 48 hours, regardless of the treatment given. Convalescence was usually rapid; most patients were able to return to work by the fourth day after treatment.

Parasitological Response.—The results are given in detail in the table. In tabulating the number of hours before disappearance of parasitemia, the persistence of gametocytes was not included. Although precise records on gametocyte clearance were not kept, our impression does not differ from the accepted concept that the 4-aminoquinoline compounds are only weakly gametocidal. P. vivax gametocytes usually disappeared promptly, but P. falciparum gametocytes often persisted until after further treatment with primaquine (8-4 [amino-1-methylbutylamino]-6-methoxyquinoline) or pentaquine (8-[5-isopropylaminoamylamino]-6-methoxyquinoline).

Results of 600 Single Dose Treatments with Amodiaquine and Chloroquine*

Doses, Gm. of Base	Total Number of Patients	P. Falciparum Infection			P. Vivax Infection		
		Number of Patients	Average Number of Hrs. Until		Number of Patients	Average Number of Hrs. Until	
			Temperature Remained Normal	Parasitemia Disappeared		Temperature Remained Normal	Parasitemia Disappeared
Amodiaquine	380	185	....	....	195	....	....
1.0	75	33	13.2	26.3	42	15.3	27.5
0.8	80	40	18.5	34.6	40	14.6	25.6
0.6	125	62	17.7	31.1	63	17.8	25.0
0.4	100	50	19.8	30.7	50 (3)†	18.2	27.6
Chloroquine	220	97	....	....	123	....	....
0.6	100	41 (1)	20.0	30.2	58	17.4	22.1
0.45	120	52 (3)	31.4	41.9	63 (2)	19.2	28.5

* Later relapses are not indicated in this table.
† The figure in parentheses represents the number of cases in which the response to the single dose treatment was not satisfactory.

Treatment Failures.—Among the 220 persons who received chloroquine, there were 6 who did not respond to this treatment (one from the 0.6 gm. schedule, the others from the 0.45 gm. group). These six persons continued to have schizonts in the peripheral blood as well as elevation of temperature and other clinical symptoms that necessitated re-treatment. All responded satisfactorily to a three-day chloroquine regimen. Among the 380 individuals included in the amodiaquine groups, there were 3 who did not respond, all of whom had been treated by the 0.4 gm. schedule; they responded promptly to re-treatment with 1.0 gm. of amodiaquine. The distribution of these failures is included in the table.

Relapses.—The known number of relapses is small. Only 12 persons reported back to the hospital or outpatient dispensaries with return of symptoms and parasitemia. All had had malaria due to P. vivax. Four of these had been treated with 0.4 gm. of amodiaquine, five with 0.45 gm. of chloroquine, and three with 0.6 gm. of chloroquine. It is possible that some others may have taken antiplasmodial drugs on return of fever without coming to our attention in the hospital or at the dispensaries. The number of these is believed to be small, however, because most of these persons are too poor to privately purchase antimalarial medicines.

Toxicity.—In the dosages administered, no serious toxic effects were noted. Five of the amodiaquine-treated patients and four of the chloroquine-treated patients vomited after administration of the drug; in all of these, the tablets were well tolerated when administration was repeated, and so it is more logical to ascribe the vomiting to the disease than to the medicaments. Both compounds were administered to persons with malaria complicated by a number of other conditions, such as cardiovascular disease, marked malnutrition or cachexia, hepatic or renal disease, pulmonary diseases, and advanced pregnancy. In no instance was there clinical evidence of drug toxicity or intolerance.

COMMENT

It should be emphasized that this study was done in an area where malaria is endemic and the adult native population is presumably highly immune. Results of treatment among a nonimmune population or among an immune population of another location may be less favorable than our results, or might be better. Variation in parasite strain may also produce responses not completely in line with our observations.

In this locality it appears to be practical to treat most patients with malaria on an ambulant basis with very few tablets of either amodiaquine or chloroquine in a single oral dose. Probably this will prove to be true for many other endemic areas in the world, and in these areas such treatment will be economical of money, time, and hospital facilities. However, we do not advocate ambulant treatment for all cases; patients with P. falciparum infections, particularly, should be hospitalized for 36 to 48 hours whenever this is possible in order to better cope with potential complications.

The time for disappearance of parasites from the blood is stated conservatively in all instances. Since blood films were made only two times a day, at 6 a. m. and at 3 p. m., the disappearance of parasites would only occasionally be noted shortly after its actual occurrence; frequently a lapse of a few hours could be presumed between the actual disappearance of parasites and its demonstration at the next regular time for blood examination.

None of the patients received any medication parenterally. Amodiaquine has been used parenterally with success [3] elsewhere, and chloroquine has been employed intravenously, with success here in Honduras.[4] It is essential that reliable préparations such as these that can be given parenterally be always available for treatment of those severely ill patients who, because of coma or vomiting, are unable to take the medication orally.

SUMMARY

Six hundred Hondurans were treated for malaria with a single oral dose of either amodiaquine (camoquin®) or chloroquine (aralen®). Four amodiaquine doses were used among 380 patients: 0.4 gm., 0.6 gm., 0.8 gm., and 1.0 gm. of the base. Two chloroquine schedules were employed among 220 patients: 0.45 gm. and 0.6 gm. of the base. All of the amodiaquine groups as well as the 0.6 gm. chloroquine group showed satisfactory clinical and parasitological responses. The response in the 0.45 gm. chloroquine group did not prove entirely satisfactory.

Only 9 individual treatment failures were observed among the 600 patients. Six patients had received small amounts of chloroquine (0.45 or 0.6 gm. of base), and three had received 0.4 gm. of amodiaquine. These cases do not include those in which there was persistence of gametocytes in the peripheral blood, which occurred in a small but unknown number of additional persons. Twelve relapses of P. vivax malaria were observed. Four of these occurred after treatment with 0.4 gm. of amodiaquine and the others occurred after small doses of chloroquine (0.45 gm. or 0.6 gm.). The toxic side-effects of both compounds are insignificant with the dosages used. Obviously, it is of great advantage to have two antiplasmodial agents that are applicable to mass treatment with a single small oral dose.

3. Payne, E. H.; Sharp, E. A., and Nickel, K. C.: Parenteral Use of Camoquin Hydrochloride as an Antimalarial, Am. J. Trop. Med. **29**: 353, 1949. Payne, E. H., and others: Intravenous Amodiaquin (Camoquin) in Naturally Acquired and Induced Malaria, ibid. **31**: 698, 1951.

4. Scott, V.: Single Intravenous Injections of Chloroquine in the Treatment of Falciparum Malaria: Toxic and Immediate Therapeutic Effects in 110 Cases, Am. J. Trop. Med. **30**: 503, 1950.

A STUDY OF RUBBER ADHESIVES IN SHOES AS THE CAUSE OF DERMATITIS OF THE FEET

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and
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Dermatoses of the feet are troublesome and rather common. They range from mild fissuring between the toes to severe vesiculation, oozing, and edema of almost the entire foot. They may be of short or long duration. They may be sufficiently severe so that a physician is consulted early in the course of the disease, or they may be mild enough to have been self-medicated for many months before the aid of a physician is sought. The signs and symptoms of different dermatoses of the feet may be sufficiently similar so that it becomes difficult to diagnose and treat the dermatoses. It is the purpose of this paper to discuss the specific agent that causes allergic eczematous contact-type dermatitis of the feet, a condition that we believe is now being confused with epidermophytosis, bacterial infections, and inflammatory skin conditions from other causes. This condition clears readily when the allergen is eliminated. Usually we have been able to determine the specific allergen in these cases, and we can now state which allergens should be used for testing patients with such conditions.

In 1949, Gaul and Underwood [1] pointed out that many dermatoses of the feet, which are diagnosed and treated as fungous infections, are more correctly diagnosed as a dermatosis caused by an irritant or allergen in the shoes of the patient. They were able to support their opinion with positive results of patch tests to various portions of the patients' shoes. The patch test data led Gaul and Underwood to be suspicious of the adhesive materials in the shoes. They attempted to obtain more information about these materials but reported, "Letters to companies manufacturing adhesive materials brought two samples and a decided reluctance to divulge their ingredients."

Jordon [2] studied 43 cases of dermatitis of the feet and concluded that resinous shoe linings were the cause of the dermatitis, though he was unsuccessful in obtaining any positive reactions to any resin or other single ingredient in the resinous lining in any case that he studied. A study of rubber footwear as a cause of foot eczema led Bonnevie and Marcussen [3] to the opinion that the specific allergen was one or more of the accelerators of the mercaptobenzothiazole type, which were used in the manufacture of the rubber.

During the past year we have studied 24 cases of dermatitis of the feet that seemed to be caused by shoes. In each of the cases there was a history of a dermatitis that could be correlated to the wearing of one or more pairs of shoes. Positive patch test reactions to portions of the shoes were obtained to support the history in 20 of the cases. In three we were unable to test the suspected shoes. In only one were we unable to obtain a positive reaction from any of the shoe materials.

Twenty-one of the 24 patients were women, and in a large majority of them we found positive patch test reactions to the light-colored, combined, cloth linings in the

Dr. Miller is now residing in Salem, Ore.

From the Department of Dermatology, Harvard Medical School and Massachusetts General Hospital.

1. Gaul, L. E., and Underwood, G. B.: Primary Irritants and Sensitizers Used in Fabrication of Footwear, Arch. Dermat. & Syph. **60**: 649-675 (Nov.) 1949.

2. Jordon, J. W.: Contact Dermatitis Due to Synthetic Resins in Shoe Linings, Arch. Dermat. & Syph. **62**: 671-680 (Nov.) 1950.

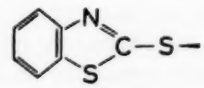
3. Bonnevie, P., and Marcussen, P. V.: Rubber Products as a Widespread Cause of Eczema: Report of 80 Cases, Acta dermat.-venereol. **25**: 163-178 (Sept.) 1944.

shoes. These combined cloth linings usually consisted of a faille and a coarser backing cloth, which were held together with a rubber adhesive. The close association of dermatitis due to shoes with dermatitis due to rubber has been discussed in each of the previously cited references. We felt that the rubber adhesive used in the combined linings might be the cause of the dermatitis, and we proceeded on this basis.

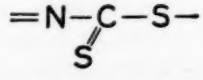
Some survey testing of the patients indicated that it was likely that they were sensitive to an antioxidant or accelerator used in the rubber adhesive, as in Bonnevie and Marcussen's [3] cases. Ten representative antioxidants and 17 accelerators [4] used by the rubber industry were made available to us, and as many of the patients as possible were tested with these materials. Numerous vesicular reactions were observed, but it became apparent that a good many of the patients reacted to none of the materials tested. Also, it was not known definitely that these particular antioxidants or accelerators were used in the fabrication of the adhesives used in the combined linings.

Subsequently a manufacturer of combined linings supplied us with the separate ingredients and combinations of ingredients that are present in the adhesives used in some combined linings. These ingredients included various kinds of rubber, an antioxidant, a tackifier, a plasticizer, a peptizing agent, and two accelerators. It soon became apparent that the patients reacted violently to the antioxidant and to any combination of ingredients containing the antioxidant. This antioxidant had not been among those previously used by us for patch tests. Some of the patients who had reacted to none of the other antioxidants or accelerators were recalled and were shown to react positively to this antioxidant. Unfortunately all patients could not be recalled for testing with the new material. This antioxidant is the monobenzyl ether of hydroquinone.

Table 1 shows the patch test data for 21 of these patients. (The three patients who showed no reactions to any of these chemicals are omitted.) Five of the 17 accelerators contain a compound possessing a mercaptobenzothiazole radical:



Four contain a compound that has a dithiocarbamyl radical:



Two are mixtures of both types of compounds. The other accelerators and antioxidants have various chemical

TABLE 1.—*Patch Test Reactions to Accelerators and Antioxidants**

Case number	Group I										Group II			Group III				Group IV			
	1†	2†	3	4	5	6	7	8	9	10	11	12	13	14†	15†	16	17	18	19	20	21
Accelerators																					
Mercaptobenzothiazole type																					
2-Mercaptobenzothiazole	−	−	−	−	−	−	−	−	−	−	+	+	−	−	+	−	−	+	+	+	−
2,2′-Benzothiazyl disulfide	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	−	−	+	+	−	−
Zinc benzothiazyl sulfide	0	−	−	−	0	0	−	0	0	0	+	+	+	−	0	0	−	0	0	0	0
Benzothiazyl sulfenamide	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	−	−	+	+	−	−
3-Anilinomethyl-2(3)-benzothiozolethione	−	−	−	−	−	−	−	−	−	−	+	+	−	+	+	−	−	+	+	−	+
Mixed																					
Zinc benzothiazyl sulfide and tetramethylthiuram monosulfide	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	+	+	+	+	−	−
A mercaptobenzothiazole and a dithiocarbamate	−	−	−	−	−	−	−	−	−	−	+	+	+	−	+	−	−	+	+	−	−
Dithiocarbamyl type																					
Tetramethylthiuram monosulfide	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	+	−	−	−	−
Tetramethylthiuram disulfide	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−
Selenium dimethyl dithiocarbamate	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
N-pentamethylene ammonium pentamethylene dithiocarbamate	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−
Miscellaneous																					
2-Mercaptothiazoline	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Diphenylguanidine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Diphenylguanidine phthalate	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Butyraldehyde-aniline condensation product	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Triethyltrimethylenetriamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Hexamethylene tetramine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Antioxidants																					
Monobenzyl ether of hydroquinone	+	+	+	+	+	+	0	0	0	0	−	−	−	+	+	+	+	0	0	0	0
S-di (β-naphthyl)-p-phenylenediamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Mono and dioctyl diphenylamines (mixture)	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Polymerized trimethyl dihydroquinoline	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Aldol alpha naphthylamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Phenyl beta naphthylamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Phenyl alpha naphthylamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−
Reaction product of diphenylamine and acetone	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
A diacrylamine-ketone-aldehyde reaction product and N,N′-diphenyl-p-phenylenediamine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Acetone and aniline condensation product	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Polyalkalated phenol sulfide	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

* − = no reaction or mild erythema; + = vesiculation; 0 = not tested.
† These patients were tested with special shoe linings (see text).

4. Mr. C. C. Davis of the Boston Woven Hose and Rubber Company supplied these materials.

structures. All the materials were tested in 1% concentration in petrolatum. The tests were made on the upper arm, were kept on the skin for 48 hours, and were read one hour after removal. Only vesicular reactions are recorded as positive; no reaction and mildly erythematous reactions are recorded as negative; and "0" indicates that the patient was not tested. These data are summarized in table 2.

The numbers in parenthesis in table 2 show the number of individual accelerators of the type indicated to which the patient showed reactions. The patients have been divided into five groups. In group I are the patients who reacted only to monobenzyl ether of hydroquinone or those whom we suspect would have reacted to this material had we been able to recall them for testing. (These latter patients had positive reactions to typical combined linings and were not sensitive to any other antioxidant or accelerator.) In group II are the patients who were not sensitive to monobenzyl ether of hydroquinone but were sensitive to the mercaptobenzothiazole or dithiocarbamyl compounds. In group III are the patients who were sensitive to monobenzyl ether of hydroquinone and to either the mercaptobenzothiazole compounds or the dithiocarbamyl compounds. In group IV are patients who were sensitive to mercaptobenzothiazole compounds and occasionally to some other compound but who were not tested to monobenzyl ether of hydroquinone. In the last group are three patients who showed no positive reactions to any of the antioxidants or accelerators. One was sensitive to a typical combined lining, one to a box toe in the shoe, and one to brown dyed leather.

TABLE 2.—*Summary of Patch Test Data**

Case No.	Shoes	Monobenzyl Ether of Hydroquinone	Mercaptobenzothiazole Type	Dithiocarbamyl Type	Others
Group I					
1†	+	+	−	−	−
2†	+	+	−	−	−
3	+	+	−	−	−
4	+	+	−	−	−
5	0	+	−	−	−
6	0	+	−	−	−
7	+	0	−	−	−
8	+	0	−	−	−
9	+	0	−	−	−
10	+	0	−	−	−
Group II					
11	+	−	+ (7)	−	−
12	+	−	+ (7)	−	−
13	+	−	+ (5)	+ (5)	−
Group III					
14†	+	+	+ (1)	−	−
15†	+	+	+ (6)	−	−
16	0	+	−	+ (2)	−
17	+	+	−	+ (4)	−
Group IV					
18	−	0	+ (6)	−	−
19	+	0	+ (6)	−	−
20	+	0	+ (1)	−	+ (1)
21	+	0	+ (1)	−	+ (2)
Group V					
22	+	−	−	−	−
23	+	−	−	−	−
24	+	−	−	−	−

* − = no reaction or mild erythema; + = vesiculation; 0 = not tested. Numbers in parentheses indicate the number of accelerators of the type indicated to which the patient reacted.
† These patients were tested with special shoe linings (see text).

It is our opinion that monobenzyl ether of hydroquinone is frequently the allergen in dermatoses that arise from the combined linings of shoes. The patients who were sensitive to this antioxidant often gave a history of dermatitis from other rubber articles (garters, elastic, rubber tubing used for a tourniquet, and adhesive plaster). Patients who reacted to the antioxidant, monobenzyl ether of hydroquinone, obtained from a rubber company, also reacted to the pure chemical, monobenzyl ether of hydroquinone, as obtained from the Eastman Kodak Company. This would tend to rule out the possibility that the patients might be reacting to an impurity in the antioxidant. They often showed a severe vesicular reaction to a concentration of 1 part of the chemical in 10,000 parts of petrolatum. Those whom we have tested do not react to hydroquinone.

The combined lining manufacturer made two linings for us, which were the same in all respects except that one contained monobenzyl ether of hydroquinone and an accelerator of the mercaptobenzothiazole group and the other contained neither of these materials. All other ingredients were identical in the two linings.

These linings were fabricated into shoes,[5] one lining in the right shoe and the other lining in the left. Pairs of these shoes were given to four patients (cases marked with a dagger [†] in groups I and III). The patients were not told that the linings were different, nor could they tell any difference from looking at the linings. They were asked to wear the shoes for short periods of time and report to us. Each patient showed vesicles on the dorsum of the foot on which was worn the shoe made from the lining containing monobenzyl ether of hydroquinone and the mercaptobenzothiazole accelerator. This vesiculation occurred 12 to 24 hours after the shoes had been worn for approximately 30 minutes. The other foot remained normal.

It would not be possible from this experiment to determine whether the monobenzyl ether of hydroquinone or the accelerator was the allergen for two patients (cases 14 and 15), since they were sensitive to both substances. For two others (cases 1 and 2), however, monobenzyl ether of hydroquinone must be the allergen, since these two patients were not sensitive to the accelerator.

COMMENT

Monobenzyl ether of hydroquinone is the antioxidant that was reported by Oliver, Schwartz, and Warren [6] to have caused leukoderma among tannery workers who wore rubber gloves that contained this antioxidant. There have been other reports [7] of the depigmentation that this compound causes. The ability of this compound to cause allergic hypersensitivities has not been stressed. Schwartz [8] stated that, on trying to cause depigmentation of his own skin, he caused an eczematous-type reaction. In the discussion of the Oliver, Schwartz, and Warren

5. The United Shoe Machinery Corporation, Beverly, Mass.
6. Oliver, E. A.; Schwartz, L., and Warren, L. H.: Occupational Leukoderma, Arch. Dermat. & Syph. **42**: 993-1014 (Dec.) 1940.
7. Spencer, G. A.: Leukoderma Produced by Antioxidants: Report of Cases, Arch. Dermat. & Syph. **58**: 215-219 (Aug.) 1948. Bernstein, E. T., and Sachs, P. M.: Pigmentary Disturbance Following Exposure to Monobenzyl Ether of Hydroquinone, ibid. **59**: 542-548 (May) 1949.
8. Schwartz, L.; Oliver, E. A., and Warren, L. H.: Occupational Leukoderma, Pub. Health Rep. **55**: 1111-1130 (June 21) 1940.

paper,[6] Sulzberger stated that, in an attempt to cause depigmentation with monobenzyl ether of hydroquinone by experimental patch tests, he produced an eczematous, allergic specific sensitization in "approximately 50 per cent of the cases" by the application of full-strength monobenzyl ether of hydroquinone. Lockhart and Loewenthal[9] commented, "Although the reaction of contact-type, eczematous dermatitis is obtained by patch testing, several authors believe that depigmentation may occur without such initial reaction." Botvinick[10] reported a case of leukoderma and dermatitis from a pair of rubber gloves that were shown to contain monobenzyl ether of hydroquinone. We seldom saw evidence of depigmentation in any of our patients. It is true, however, that we did not follow many of these patients for very long after the acute phase of the dermatitis had subsided.

Monobenzyl ether of hydroquinone has been studied mostly with respect to its depigmenting action among rubber workers and wearers of rubber articles. Its eczematizing action has been observed during attempts to cause depigmentation experimentally. Allergic, eczematous, contact-type dermatitis among wearers of rubber articles containing monobenzyl ether of hydroquinone has been less frequently reported. The manufacturer of this material has reported to us that no dermatitis has occurred among the workmen who handle this antioxidant. Nevertheless, we suspect that its sensitizing index is relatively high when it gets into contact with the skin in shoes or adhesive plaster, though certainly not nearly as high as the 50% reported by Sulzberger in his small patch test series. It seems sufficiently high so that every effort should be made to prevent the use of monobenzyl ether of hydroquinone in rubber articles that come into contact with the skin.

Allergic, eczematous contact-type dermatitis to other antioxidants and accelerators that we tested is less frequent. It must not be concluded that those compounds that showed completely negative reactions in this group of patients are safe compounds to use. It may be that these patients had not previously been in contact with these compounds and that, therefore, they would not be expected to show a reaction to them. A good example of this situation is the compound hexamethylenetetramine, an accelerator that is seldom used by the rubber industry today. It has been discarded because it was found to have a high index of sensitization. Also, it must be remembered that substances that are not allergenic for this group of patients might sensitize even a higher percentage of persons from the population at large.

In a suspected case of dermatitis caused by shoes it is certainly not necessary to test to the large group of materials we used. Three types of compounds could be used: (1) monobenzyl ether of hydroquinone, (2) 2-mercaptobenzothiazole, and (3) tetramethylthiuram monosulfide. If these three compounds are used, it is probable that reactions will be found to one or more of them if the shoe dermatitis is caused by one of the rubber ingredients of the shoes.

We wish to emphasize the opinion previously expressed by Gaul and Underwood[1] that, when a patient is seen with a dermatitis of the feet, it is important to remember that the dermatitis may result from an allergic hypersensitivity to some ingredient in the shoe. In the cases of this type that we have studied, the most frequently observed allergen was an antioxidant or accelerator used in the rubber adhesives in the shoes.

SUMMARY

An acute dermatitis of the feet may be an allergic, eczematous, contact-type dermatitis. The allergen for those patients we have studied was most frequently the antioxidant monobenzyl ether of hydroquinone, which is used in the rubber adhesive in the combined linings of the shoe. Some of these patients were specifically sensitive to other rubber antioxidants and accelerators.

Fruit St. (14) (Dr. Blank).

9. Lockhart, R. J. J., and Loewenthal, L. J. A.: Occupational Leukoderma: A Report of 6 Cases Observed in a South African Factory, South African M. J. **23**: 867-868 (Oct. 22) 1949.

10. Botvinick, I.: Dermatitis and Secondary Leukoderma Due to Fabric-Lined Rubber Gloves: Report of a Case, Arch. Dermat. & Syph. **63**: 334-335 (March) 1951.

STERILITY OF MARKET COTTON

John H. Silliker, Ph.D.
and
Eugene P. Hess, M.S., Los Angeles

The consumer's guarantee of sterility in products labeled "sterile" lies chiefly with the producer. In the case of "sterile" market cotton,[1] the control program of the Food and Drug Administration, in the Los Angeles area at least, consists of taking random samples at periodic intervals. These are sent to the Federal Drug Administration in Washington, D. C., for sterility testing. Results of these investigations are not available. In view of this, it was decided to make a survey of "sterile" market cotton to determine whether the present control program is adequate to insure sterility in all packages of cotton.

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1. Purified cotton (sterile absorbent) U. S. Pharmacopeia XIV.

EXPERIMENTAL DATA

Procurement.—Samples of "sterile" market cotton were purchased from retail stores in various parts of the city of Los Angeles. Generally a single 4-oz. roll of a nationally prominent brand was purchased from each retailer. At the time of purchase, no mention was made of the survey being conducted. Only undamaged packages, labeled "sterile," were used.

Sampling.—For the purpose of sampling, a large transfer chamber containing a Westinghouse sterile lamp

was used. The chamber was completely enclosed except for hand inserts. Previous to use, the chamber was completely swabbed with a technical grade of benzalkonium chloride (roccal,® 1: 1,000 solution). All sampling procedures were carried out under ultraviolet rays.

The outside of each package of cotton was thoroughly wetted with benzalkonium chloride before being placed in the transfer chamber. The moist package was exposed to the ultraviolet rays for at least 10 minutes before the outer covering was broken. This allowed for complete drying in a sterile environment. The cotton roll was removed from the package, and the paper enclosing the roll was swabbed with benzalkonium chloride. The first sample was taken from the end of the roll, and subsequent samples were taken at intervals of approximately 12 in., moving toward the center of the roll. In total, five samples were obtained from each 4-oz. roll.

Sterile applicator sticks were handled with hemostats, which were previously allowed to stand in benzalkonium chloride for a period of three minutes and then flamed before use. An amount of cotton, approximating that used for a throat swab, was twisted on the end of the stick. The stick was then broken at a point above the sample, with sterile hemostats used for all manipulations, and the swab was dropped into an 8-oz., wide mouth, sterile bottle containing approximately 50 ml. of sterile fluid thioglycollate medium (as recommended in the U. S. Pharmacopeia for sterility tests). Previous to use the outer surfaces of the culture bottles were swabbed with benzalkonium chloride, and the bottles were then allowed to stand in the chamber for 10 minutes.

The bottles containing the medium were incubated for 48 hours at 37 C previous to inoculation as a check on the initial sterility for the medium. Along with each roll sampled, a control bottle was inoculated with a 3-cm. section of a sterile applicator stick that was handled in exactly the same manner used for all other samples taken. It must be emphasized that the control bottle for each roll of cotton tested was inoculated in the same atmosphere as the test samples and had equal opportunity for chance contamination.

The samples thus obtained were incubated at 37 C for three weeks and examined at weekly intervals. Those bottles showing turbidity were checked for the presence of micro-organisms by means of microscopic observation of gram-stained smears. The viability of the organisms was determined by subculture on nutrient agar.

Results.—Table 1 summarizes the results obtained from the examination of 85 different rolls of market cotton. It can be seen that in 14 out of 413 different samples viable organisms were detected. Twelve out of 85 rolls of cotton contained viable micro-organisms. In two instances two positive results were obtained from the same roll. Of the 14 samples containing viable organisms, one was obtained from the outermost portion of the roll; five were obtained 1 ft. from the outside; four were obtained 2 ft. from the outside; two were obtained 3 ft. from the outside; and two were obtained from the innermost center of the roll. As nearly as could be determined the positive samples each contained a single type of bacteria. Gram-positive cocci were found in seven samples, gram-negative, non-spore-forming rods in three, a gram-positive, anaerobic, spore-forming rod in one, a gram-negative spore-forming rod in another, and the gram-positive rods in two.

ISOLATION AND DETERMINATION OF HEAT RESISTANCE OF CONTAMINANTS FOUND IN MARKET COTTON

Four of the positive samples were selected for further study. Pure cultures were obtained from the thioglycollate broth with the use of the loop dilution and streak plate techniques. The cultures thus obtained were as follows: no. 49, short, gram-negative, non-spore-forming, aerobic rods; no. 52, gram-positive micrococci (albus type); no. 58, short, gram-positive rods showing extreme pleomorphism with a definite tendency to show coccoid forms; and no. 63, gram-negative, aerobic, spore-forming rods.

For the determination of the heat resistance of the above isolates, the organisms were grown at 28 C in bottle slants containing nutrient agar and harvested at the point of maximum growth. The cells were suspended in M/20 phosphate buffer with a pH of 7.0, washed twice by centrifugation, and resuspended in the buffer. Plate counts were made from the final buffer suspension.

TABLE 1.—*Results of Sterility Tests on Market Cotton* *

Brand	No. of Rolls Examined	No. of Samples	No. of Controls	No. of Positive Samples Showing Viable Organisms	No. of Positive Controls Showing Viable Organisms
A	15	75	15	2	0
B	15	75	15	5	0
C	15	75	15	2	0
D	15	75	15	2	0
E	15	75	15	3	0
F	3	15	3	0	0
G	6 †	18	6	0	0
H	1 ‡	5	1	0	0
Total	85	413	85	14	0

* Unless otherwise indicated all rolls are 4 oz.
† Two-ounce roll.
‡ One-pound roll.

Thermal death time tubes were made by sealing off one end of an 8-in. section of 8-mm. soft glass tubing. After the open end of these tubes were plugged with cotton, the tubes were sterilized in the autoclave. Into each of these tubes 1 ml. of the cell suspension was pipetted aseptically, and the open end of the tube was then sealed. The tubes were held at room temperature for 15 minutes and then immersed in an oil bath at 80 C plus or minus 0.5 C. At 5, 10, 15, 20, 30, and 60 minutes tubes of the test organisms were removed from the bath. The tubes were opened aseptically and the cell suspension poured into a Petri dish and mixed with nutrient agar. Plates were incubated for 96 hours at 28 C and observed for growth.

The results are shown in table 2. It can be seen that no. 52 survived for 60 minutes at 80 C, while 63 survived for more than 60 minutes at 80 C. The other two cultures did not survive the shortest time interval tested. It thus appears that two of the four isolates tested can be considered heat resistant.

COMMENT

Of the 415 samples taken, 14 were shown to contain viable organisms. All samples were obtained from packages labeled "contents sterile until package is opened." In terms of rolls, 12 out of 85, or 14.2%, were contam-

inated. It should be emphasized again that all precautions were taken to prevent extraneous organisms from entering the bottles of sterile medium. None of the control bottles (85 in all), which were handled in the same manner as the bottles inoculated with samples, gave positive results. If the positive samples were the result of air contamination of the medium, one would expect at least a few of the controls to show the presence of viable organisms. The conclusion is forced that the cotton itself was the source of the bacteria.

TABLE 2.—*Heat Resistance of Bacterial Contaminants Isolated from Market Cotton*

Organism	Description	Plate Count	Survival Time
49	Gram-negative, short rod	630,000,000	Less than 5 min.
52	Gram-positive cocci	6,100,000	More than 30 min., less than 60 min.
58	Gram-positive rod	85,000,000	Less than 5 min.
63	Gram-negative, short rod; spore former	2,100,000	More than 60 min.

The processing temperatures of the different producers undoubtedly vary. However, we have no information available as to the times and temperatures used. The one producer who did volunteer the information was using times and temperatures that should kill all types or organisms. However, the cotton fibers are very poor conductors of heat and as such may give protection to an organism easily killed under ordinary conditions.

These findings indicate that there should be a more stringent control program on the part of both the producers and the Food and Drug Administration in the case of "sterile" market cotton. That viable organisms were found at all different levels in the roll of cotton suggests, also, the need for a rigorous investigation into the heat insulation protection afforded to bacterial life at the center of cotton, gauze, or even a hospital surgical pack. Such studies have been made on canned foodstuffs and have, in many ways, revolutionized the food-processing industry.

SUMMARY

Market cotton labeled "sterile" was found to contain viable micro-organisms. Thermal death time studies on certain of the contaminating organisms indicated that in some cases heat resistant forms were present, while other organisms were heat sensitive and must have survived the sterilization process as a result of the protective effect of the cotton fibers or because of understerilization of the product. In view of the results obtained, it is concluded that the present control program is not adequate to assure the consumer of the sterility of each package of market cotton.

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HORMONAL MANAGEMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA

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The purpose of this paper is to report a new method for reducing the tendency to hemorrhage in patients with hereditary hemorrhagic telangiectasia (Osler-Rendu disease). Although the periods of observation of the patients treated were of short duration, the longest having been just over one year, the results to date of writing were of sufficient interest to merit a preliminary report.

DEFINITION

The term hereditary hemorrhagic telangiectasia was first advocated by Hanes [1] in 1909. He defined this disease as a "hereditary affection manifesting itself in localized dilatations of the capillaries and venules forming distinct groups of telangiectases which occur upon the skin of the face, nasal and buccal mucous membranes, and give rise to profuse hemorrhage either spontaneously or as a result of trauma." The cardinal findings for the establishment of the diagnosis of this disease are contained in Hanes' definition: (1) the hereditary tendency toward the disease, (2) the presence of typically distributed telangiectatic areas, and (3) the tendency for the telangiectatic areas to bleed. Although the hereditary factor is usually elicited from the patient's history, Fitz-Hugh [2] was the first to call attention to certain patients with no characteristic family history. He explained this on the basis of atavism or "skipped generations" in the inheritance of this disease.

The telangiectases may occur on any of the mucous membranes or anywhere on the external surface of the body. The nasal mucous membrane is oftenest affected, with tongue, palate, lips, buccal area, gum, pharynx, and conjunctiva following in order of disease incidence. The larynx, colon, lung, stomach, liver, bladder, and brain are also affected, but owing to their relative inaccessibility the reported incidence may be less than that actually occurring. On the skin the lesions are found on the face, trunk, arms, finger tips, and nail beds. Aneurysm of the pulmonary artery has been reported by Rundles,[3] but the relation of vascular anomalies to this disease is uncertain. No evidence for a blood dyscrasia except that associated

Drs. William MacComb, Oliver Moore, and William Money, and Miss Martha von Lackum assisted in the preparation of this paper.

The ethinyl estradiol (estinyl®) and "gynetone" (a tablet containing estradiol and methylestosterone in a 1:10 ratio) used in this study were supplied by Schering Corporation, Bloomfield, N. J.

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1. Hanes, F. M.: Multiple Hereditary Hemorrhagic Telangiectasia Causing Hemorrhage (Hereditary Hemorrhagic Telangiectasia), Bull. Johns Hopkins Hosp. **20**: 63-73, 1909.

2. Fitz-Hugh, T., Jr.: The Importance of Atavism in the Diagnosis of Hereditary Hemorrhagic Telangiectasia, Am. J. M. Sc. **166**: 884, 1923.

3. Rundles, R. W.: Hemorrhagic Telangiectasia with Pulmonary Aneurysm, Am. J. M. Sc. **210**: 76-81, 1945.

with chronic blood loss has been noted. The telangiectases begin as dilatations of the capillaries and have a bright red color. As these areas increase in size, the venules participate in the ectasia, giving the cutaneous lesions a violaceous color. The telangiectases of the mucous membranes are always a brilliant red. According to Hanes,[1] the papillae of the corium are obliterated, with loss of the undulations of the stratum germinativum. Immediately subjacent to the attenuated epidermis are wide blood spaces lined by a single layer of endothelium and without either an elastic or a muscular coat.

CLINICAL SUMMARY

The commonest symptom of the disease is epistaxis, but other mucous membranes or the skin may be the exclusive sites of hemorrhage. Hematemeses, hemoptyses, melena, hematuria, and cerebrovascular accidents may occur. Anemia often results from the long-continued blood loss, and fatal hemorrhages have occurred. Trauma is not the only cause of bleeding, for it may occur spontaneously or may arise from irritation or congestion. The telangiectases usually do not appear before the age of puberty. In the third and fourth decades of life they become more numerous and more subject to hemorrhage.

Treatment of this condition has been well summarized by Peluse.[4] Medical management has largely been directed to the control of frequent severe epistaxes. The measures used include the application of caustic agents to the nasal mucosa, submucosal injections of sclerosing solutions such as quinine, ethyl carbamate, and sodium psylliate (sylnasol®), or the use of hemostatic yarn or gauze as nasal packing. Surgical amelioration has been directed to the ligation of the external carotid arteries or anterior ethmoidal arteries and to electrocauterization of the nasal septum and turbinates. X-ray therapy and radium applications to the nasal passages have been of no benefit and have often produced atrophic rhinitis and frequently have caused the sloughing of large areas of the nasal septum. General measures include the injection of moccasin snake venom to increase blood coagulability, and, more recently, favorable reports have followed the use of vitamin P (rutin).[4] Change of climate has been advised in an effort to decrease the incidence of acute coryza with associated nasal hemorrhages. Whole blood transfusions and iron replacement therapy have been required constantly to correct the secondary anemia that usually occurs. No single therapeutic agent or surgical approach, or combination of them, has heretofore consistently decreased the incidence or severity of recurrent hemorrhage. Below are presented the case reports of five patients with hereditary hemorrhagic telangiectasia whose tendency to bleed was reduced with estrogen therapy.

REPORT OF CASES

CASE 1.—A 44-year-old woman had a familial history of hereditary hemorrhagic telangiectasia. Her epistaxes began just prior to her menarche at the age of 15. For many years thereafter epistaxes occurred during the five days prior to the onset of menstruation, then disappeared on the first day of her menstrual period. Many local therapeutic measures, including electrocautery, sodium morrhuate injections, submucous resection, and radium implantation, were unsuccessful in alleviating her condition. In 1948, when she was 42, roentgen castration was performed in an attempt to control the epistaxes. There was an immediate radiation reaction, characterized by nausea, vomiting, and cramping abdominal pain. No menstrual periods occurred thereafter. Immediately following this artificial menopause, the patient noted an increase in the severity and incidence of the epistaxes. They became completely acyclic in character and remained so until the time of her admission to Memorial Center on Dec. 13, 1950.

On admission, physical examination revealed the typical telangiectases of Osler-Rendu disease distributed over the tongue, mouth, and nasal mucous membranes. The nasal mucosa was edematous, crusted, and relatively avascular (except for the telangiectatic areas). An extensive perforation of the nasal septum from previous surgery and irradiation was noted.

Laboratory studies revealed a hemoglobin level of 8.0 gm. per 100 cc., a red blood cell count of 2,900,000, and a white blood cell count of 9,500 with a normal differential count. The hematocrit was 29%. Reticulocytes were 1.1%; platelets, 397,000. Bleeding time was 1½ minutes; clotting time, 12 minutes; prothrombin time, 17.9 minutes. Urinalysis was within normal limits. A urinary gonadotropic, follicle-stimulating hormone assay was positive for 104 mouse units and negative for 208 mouse units per 24 hours. (This is within the postmenopausal range by the method used.[5])

The patient received 1,000 cc. of whole blood on Dec. 15, 1950, and again on Dec. 18. The next day the hemoglobin level was 11.2 gm. per 100 cc. Because of the history of cyclic epistaxes and the increase in incidence and severity following roentgen castration, a course of orally administered ethinyl estradiol, 0.5 mg. twice daily, was started Dec. 22. A week later an examination of the nasal mucosa revealed a return to normal vascularity, a decrease in edema, and the absence of crusting or bleeding points. Epistaxes disappeared, and the patient became asymptomatic. She was discharged Jan. 5, 1951. Beginning Jan. 12 and continuing for the next week, the patient noted ankle edema and an increase in body weight. On Jan. 18 she was readmitted, and ethinyl estradiol was discontinued. An immediate diuresis occurred, and the patient remained asymptomatic until Jan. 27, when vaginal bleeding occurred. Epistaxes recurred on Feb. 2 and 4. On examination it was noted that the mucous membranes had returned to their pretherapy state. Ethinyl estradiol, 0.25 mg. per day, was given again on Feb. 5. The patient was discharged on March 1, while still receiving the drug, having been asymptomatic since Feb. 10.

Response to treatment continued until Sept. 17, 1951, when, on the advice of her local physician, the patient discontinued estrogen therapy because of low abdominal discomfort plus soreness and swelling of the right breast. The red blood cell count was 4,100,000. Heavy vaginal (estrogen deprivation) bleeding began Sept. 20 and continued through Sept. 23. On Sept. 26 epistaxes began and continued spasmodically for three days. At the first sign of nasal hemorrhage the patient resumed her daily medication of 0.25 mg. of orally administered ethinyl estradiol. Epistaxes disappeared Sept. 30 and have not recurred to the present writing.

CASE 2.—A 60-year-old white man was first seen at Memorial Center on May 31, 1951. A history of repeated epistaxes of 25 years' known duration was elicited. His mother, two brothers, a son, and a daughter had all been subject to frequent and severe epistaxes. The mother and one brother died following severe hemorrhage. Three sisters of the patient had no signs or symptoms of this disease. Epistaxes began in the patient at the age of 35. They were mild, spontaneous, and recurrent every few days and were not troublesome until six years prior to his admission to Memorial Center, when they gradually became more frequent and more profuse. Local medical and surgical measures, as well as radium application to the nasal mucosa, were unsuccessful in controlling the hemorrhages.

On admission, physical examination revealed many telangiectases distributed over the face, trunk, upper extremities, tongue,

4. Peluse, S.: Gingival Hemorrhage with Oral Manifestations in Hereditary Hemorrhagic Telangiectasia: Successful Control with a Sclerosing Agent Sylnasol: Effect of Vitamin P and Nicotinic Acid: Role in Case Reported Which Was Observed 5 Years, Arch. Otolaryng. **44**: 668-685 (Dec.) 1946.

5. Method of Kleinfelter, Albright, and Griswold in Smith, P. H.; Albright, F., and Dodge, E.: Modifications in Methods for Precipitation and Assay of Increased Amounts of Pituitary Gonadotropic Substances in Urine, J. Lab. & Clin. Med. **28**: 1761-1766, 1943.

and mouth. There was a large anterior perforation of the nasal septum due to previous radiation therapy. The mucous membrane of the nose was pale and edematous, with small hemorrhagic spots on the turbinates. Laboratory findings showed a hemoglobin level of 10.7 gm. per 100 cc., a red blood cell count of 3,800,000, and 247,000 platelets. The bleeding, clotting, and prothrombin times were within normal limits. A urinary gonadotropin assay was positive for 104 mouse units and negative for 208 mouse units per 24 hours, an abnormally high value for men. The 17-ketosteroids (total neutral fraction) were 9.4 and 8.0 mg. per 24 hours. Blood chemistry studies, including serum chloride, sodium, potassium, total protein, cephalin flocculation, and thymol turbidity tests, were all within normal limits.

Administration of ethinyl estradiol, 0.25 mg. daily, was started June 7, 1951. There was no change in the frequency or severity of the patient's epistaxes until June 16, when a severe epistaxis occurred, and the patient was admitted to the University of Pennsylvania Hospital for nasal packing and transfusion. At that time an examination revealed a decrease in the size of the facial telangiectases. There was no change in the nasal mucous membranes.

The patient was readmitted to Memorial Center June 25, at which time the dose of ethinyl estradiol was increased to 0.5 mg. daily. Laboratory studies revealed a hemoglobin level of 12.1 gm. per 100 cc., a red blood cell count of 4,300,000, and a white blood cell count of 9,700 with a normal differential. Liver function studies, including cephalin flocculation, thymol turbidity, total protein, and albumin-globulin ratio, were within normal limits. On June 28 the nasal packing was removed without bleeding. The nasal mucous membranes were pink, glistening, and without evidence of telangiectases. The patient continued to be asymptomatic and was discharged on June 29, 1951, while still receiving therapy. One week later epistaxes recurred, then subsided spontaneously with no further recurrence.

A reexamination Aug. 20 revealed tenderness and swelling of both breasts, with loss of libido. Treatment was therefore changed to orally administered ethinyl estradiol, 0.5 mg. plus 5 mg. of methyltestosterone daily. Breast discomfort disappeared, and libido improved. On Oct. 22 the platelets were 86,000; by Dec. 10, 1951, they had increased to 170,000 without change in medication. The patient has remained asymptomatic to the present writing.

Case 3.—A 47-year-old white woman was admitted to Memorial Center in March, 1951, complaining of frequent epistaxes and melena accompanied by abdominal cramps and weakness. Both her grandmother and mother had telangiectases of the face and finger tips and also frequent episodes of epistaxis. The patient had occasional epistaxes in childhood. Her menarche occurred at 12 years of age. No unusual bleeding episodes were noted during the years of regular cyclic ovarian function. In 1936, when she was 32 years of age, a hysterectomy and bilateral salpingo-oophorectomy were performed for uterine fibroids, following which menopausal symptoms appeared. Shortly after this procedure, facial and thoracic telangiectases developed.

The patient was first seen at Memorial Center in 1939, at which time a diagnosis of Osler-Rendu disease was made and the facial lesions were treated with dry ice. Nasal hemorrhages were not incapacitating until 1947, when very frequent epistaxes developed that were refractory to all medical and surgical measures. In 1949 irregular gastrointestinal bleeding developed. The patient was readmitted to Memorial Center in February, 1951, because of incapacitating nasal and gastrointestinal bleeding. Following discharge, this patient was referred to the experimental hematology section for consideration of estrogen therapy.

On March 7, 1951, physical examination revealed the typical telangiectases of Osler-Rendu disease. They were distributed over the face, trunk, and upper extremities. The nasal mucous membrane was pale, atrophic, and crusted with blood. Examination was, otherwise, noncontributory. Laboratory studies on March 7 revealed a hemoglobin level of 12.3 gm. per 100 cc., a red blood cell count of 4,500,000, and a white blood cell count of 6,300 with a normal differential count. The platelet count was 360,000. The bleeding, clotting, and prothrombin times were within normal limits. A urinary gonadotropin assay on March 30 was positive for 104 mouse units and negative for 208 mouse units, a normal value for a postmenopausal woman.

On March 13, therapy with orally administered ethinyl estradiol, 0.25 mg. daily, was started. Within 10 days after institution of hormone therapy, epistaxes and gastrointestinal bleeding diminished. In one month a distinct reduction in number, size, and erythema of cutaneous telangiectases was evident. In May, 1951, two months after the institution of hormone therapy, a cyclic pattern in treatment response was noted. While receiving orally administered ethinyl estradiol, 0.25 mg. daily, the patient was in comparatively good health for three weeks. With no change in dosage, spontaneous diuresis occurred, followed in a few hours by exacerbation of bleeding and increased prominence of the telangiectases. The episode lasted for approximately one week and was followed by a three week period of favorable response. The patient was hospitalized from June 18 through June 27 for a trial period without treatment. There was prompt return of severe bleeding and telangiectases.

In August, 1951, an episode of diuresis recurred. At the same time increased epistaxes and increased prominence of telangiectases were noted. The dose of ethinyl estradiol was temporarily increased to 0.25 mg. twice daily, with prompt amelioration of these signs and symptoms. Ethinyl estradiol, 0.25 mg. daily, was resumed and was effective for the subsequent three weeks. The patient has been taught to recognize this cyclic change in response, and she varies the dosage promptly, with resultant minimal signs and symptoms.

Case 4.—A 53-year-old white man had three or four episodes of epistaxis in childhood. During the 15 years preceding admission the epistaxes had become increasingly severe, with episodes one to three times daily. About 10 years preceding admission he had had radium treatment to the nasal cavity. Since then the nasal hemorrhages had been treated by chemical and electrical cauterizations and, more recently, by ligations of the anterior ethmoidal and external carotid arteries. None of these measures had reduced the bleeding. Most of his hemorrhages occurred at night and were preceded by prodromes of nuchal pain and fulness in the frontal region. No family history of bleeding tendency was elicited.

Physical examination revealed typical stigmas of hereditary hemorrhagic telangiectasia of the face and violaceous lesions of the tongue and hard palate. The nasal mucosa was edematous and pale, with scattered lesions on the septum and turbinates and marked crusting. The heart was enlarged both clinically and roentgenologically, although the lung fields were clear. Abdominal examination revealed a palpable liver edge 2 cm. below the costal margin in the right midclavicular line (though dietary history was adequate and alcoholic intake was denied). Rectal examination revealed a symmetrically enlarged, boggy prostate. Laboratory studies prior to therapy revealed a red blood cell count of 4,200,000, a white blood cell count of 5,300, a platelet count of 256,200, and a hemoglobin level of 11.7 gm. per 100 cc. Bleeding time was 2 minutes; clotting time, 10 minutes; prothrombin time, 16.1 minutes. Liver function studies showed a sulfobromophthalein (bromsulphalein®) sodium retention of 23%, while cephalin flocculation was negative in 24 hours and 1+ in 48 hours. Thymol turbidity was 1.29 units. Total protein was 7.0 gm., with a normal albumin-globulin ratio. Acid phosphatase was 0.2 Bodansky units, and the alkaline phosphatase was 13.6 Bodansky units. Urinary gonadotropin assay was positive for 6.5 and negative for 13 and 52 mouse units per 24 hours. (This is a normal value for the male by this method.[5]) The 17-ketosteroids (total neutral fraction) were 7.4 mg. per 24 hours.

On July 10, 1951, therapy with orally administered ethinyl estradiol, 0.25 mg. daily, was started. There was no change in the incidence or severity of epistaxes during the first two weeks of treatment. During the next two weeks epistaxes gradually diminished in volume and by Aug. 6 had ceased. At that time, however, the patient complained of lassitude, loss of libido, breast tenderness, dyspnea, and ankle edema. Treatment was changed on that date to ethinyl estradiol, 0.5 mg. plus methyltestosterone 5.0 mg. daily. In addition, he was placed on a low salt diet. He was next seen on Aug. 20, by which time breast tenderness, dyspnea, ankle edema, and loss of libido had disappeared. Also, a decrease in the size and number of telangiectases was noted. There was no change in the size of the liver, the edge of which was still palpable 2 cm. below the costal margin.

The patient remained asymptomatic until Sept. 24, 1951, on which date he had a small nasal hemorrhage. On examination the nasal mucosa was seen to be moist and pink, while the telangiectatic lesions were not visible. Two similar hemorrhages occurred Nov. 26 and Dec. 7. On Dec. 12 an upper respiratory infection developed, which was followed two days later by a severe epistaxis, during which the patient lost about 250 cc. of blood. Hemoglobin determination on Dec. 17 was 9.9 gm. per 100 cc. He received 500 cc. of whole blood the next day, and local nasal packing was applied. After his transfusion the patient noted the gradual onset of weakness, numbness, and paresthesia of the lower extremities. He was admitted to Memorial Center Jan. 2, 1952, and three 500-cc. blood transfusions were given. On Jan. 15 the hemoglobin was 13.1 gm. per 100 cc. No epistaxes occurred during this admission, and the numbness and tingling in the lower extremities gradually disappeared. He was discharged from the hospital Jan. 16, receiving a dose of 0.5 mg. of ethinyl estradiol and 5.0 mg. of methyltestosterone. He has remained asymptomatic to the present writing.

Case 5.—A 42-year-old woman with hereditary hemorrhagic telangiectasia had had epistaxes for 22 years. There was a family history of this disease, which included the patient's mother, two sisters, and a brother (who died of a fatal epistaxis at the age of 32). Telangiectases were first noted by the patient's parents just prior to her menarche at the age of 10. She was entirely asymptomatic, however, until the age of 20, when her first epistaxis occurred. During the next 10 years an occasional mild nasal hemorrhage took place, with no observed relation to her menstrual cycle. At the age of 30 an increase in the frequency and severity of nasal hemorrhages occurred, requiring iron replacement therapy for a secondary anemia. At that time the patient noted that her epistaxes took place during the week prior to the onset of menstruation.

In 1942, at the age of 33, this patient had her right ovary removed because of cystadenoma. In 1946 a supracervical hysterectomy and left oophorectomy were performed. Following this operation menopausal symptoms were noted, and epistaxes became acyclic and severer. Local therapeutic measures, snake venom, vitamin K, calscorbate® (calcium ascorbate with benzyl alcohol and dextrose), vitamin C, and rutin were unsuccessful in relieving her symptoms. In April, 1951, her first hospitalization for transfusions occurred. From that time to her first visit at Memorial Center Nov. 12, 1951, four admissions for control of her nasal hemorrhages were necessary.

Physical examination revealed multiple telangiectases distributed over the tongue and hard palate. The nasal mucous membranes were atrophic, blanched, and crusted. The remainder of the examination was within normal limits. Laboratory findings showed a hemoglobin level of 11.8 gm. per 100 cc., a red blood cell count of 4,200,000, a white blood cell count of 9,600 with a normal differential. Hematocrit was 39%; platelets were 294,000. The bleeding, clotting, and prothrombin times were within normal limits. Urinary gonadotropin assay was positive for 104 mouse units and negative for 208 mouse units per 24 hours. The 17-ketosteroids (total neutral fraction) were reported to be 7.1 mg. per 24 hours.

Preliminary studies were completed Nov. 19, and on Nov. 20 therapy with orally administered ethinyl estradiol, 0.25 mg. per day, was started. Epistaxes occurred that day and the next. Because of severe nausea, therapy with orally administered estradiol was discontinued Jan. 7, 1952, and treatment with estradiol diproprionate, 0.5 mg. given intramuscularly every other day, was started. The patient's nausea was relieved, and except for rare nasal spotting she became asymptomatic and has remained so to the present writing.

COMMENT

The present study using estrogenic hormones was undertaken because of the apparent relationship between recurrent epistaxes and the menstrual cycle in a patient (case 1) with hereditary hemorrhagic telangiectasia. Nasal hemorrhages in this patient occurred one to five days before the end of the secretory phase and disappeared shortly after the onset of the menstrual period. Following roentgen castration, hemorrhages became acyclic and increased in severity.

Because the episodes of epistaxis bore a striking relationship to the periods of decreased estrogen excretion and increased urinary gonadotropin (follicle-stimulating hormone) excretion,[6] it was theorized that estrogen replacement therapy might be of benefit in controlling the nasal hemorrhages. The hypothesis was further emphasized by the change in character of the nasal hemorrhages that occurred following roentgen castration and by the high urinary gonadotropin excretions noted on admission. Accordingly; therapy was started with a dose of 0.5 mg. of ethinyl estradiol twice daily. Since we were attempting to substitute as closely as possible for alpha estradiol and preferred an oral route, this particular preparation was chosen. The dose was empirical and was deliberately much higher than that necessary to control postmenopausal symptoms.

A change in the mucous membranes was first noted one week after the onset of therapy. They had returned to a normal pink, glistening texture, and the crusting and edema seen prior to treatment had disappeared. Epistaxes were still present at this time and continued for another week of estrogen administration. By the third week of medication epistaxes had disappeared. During the fourth week, water and sodium retention became evident in that the patient gained weight and her feet and ankles became edematous. When ethinyl estradiol therapy was discontinued at the end of the fourth week, an immediate diuresis occurred. The patient was, otherwise, asymptomatic until nine days after estrogen was withdrawn, at which time slight vaginal bleeding occurred. On the 15th day without medication, and continuing for two days thereafter, epistaxes took place with increasing severity. Examination of the mucous membranes on the 16th day revealed a return to the atrophic state noted prior to therapy.

Ethinyl estradiol therapy was resumed on the 16th day with a dose of 0.25 mg. per day. During the subsequent weeks this dose was found to be adequate to restore the nasal mucosa and control epistaxes without producing the undesirable side-effect of sodium and water retention. It was, therefore, chosen as the initial dose in the treatment of subsequent patients. In the women adequate therapeutic response occurred at this dosage level with one exception. This patient (case 3) was the one who showed cyclic variation in her episodes of epistaxis and in the number and size of her telangiectases. It was found that by increasing her dose of ethinyl estradiol to 0.25 mg. twice daily during these periods of relapse her epistaxes could be adequately controlled. All of the women had increased breast fulness while taking ethinyl estradiol, but this symptom was not troublesome. Since only one woman in the series possessed an intact uterus, no statement can be made regarding the incidence of uterine bleeding with this continuous dose of estrogen. This one patient, however, had no uterine bleeding in 14 months of daily estrogen therapy.

Both of the male patients reported on in this paper responded to estrogen therapy. They were of an age con-

6. Textbook of Endocrinology, Williams, R. H., editor, Philadelphia, W. B. Saunders Company, 1950, pp. 349-350.

sistent with the male climacteric and had noted an increase in the number and severity of their epistaxes with advancing age. One of them (case 4) revealed an abnormally high excretion of urinary gonadotropins. The same treatment dose used in the women was begun with the men, but undesirable feminizing side-effects, i. e., gynecomastia and loss of libido, were noted during the third week of therapy. A dose of 2.5 mg. of methyltestosterone was therefore added to the ethinyl estradiol medication. Because the mucous membrane response was inadequate and the epistaxes began to recur, the dose was increased to 0.5 mg. of ethinyl estradiol and 5.0 mg. of methyltestosterone. This dosage level yielded satisfactory control of the epistaxes and alleviation of the feminizing side-effects.

As indicated above, undesirable side-effects common to both men and women have occurred. Sodium and water retention, as evidenced by ankle edema and exertional dyspnea, were relieved by a 0.5 gm. sodium diet and/or diuretics. Anorexia, nausea, and, rarely, vomiting have occurred with oral estrogen administration. These symptoms, when unduly troublesome, have been relieved by the substitution of estradiol diproprionate, 0.5 mg. given intramuscularly three times weekly.

To summarize, the clinical response of the nasal mucosa to estrogen therapy is a return of the mucosa to a moist and vascular appearance. In our experience this change has occurred from one to three weeks after treatment has been initiated. Concomitant with the changes in the nasal mucosa the epistaxes are decreased in number and severity to the point of only occasional spotting. The telangiectases disappear in the nasal passages. The cutaneous lesions blanch and diminish in size. It would appear that similar changes have occurred in the intestinal tract as evidenced by a disappearance of tarry stools. The prompt relapse after cessation of therapy suggests that continuous treatment is necessary to maintain the favorable response.

The mechanisms by which estrogen therapy has reduced the tendency to epistaxes in this disease cannot be explained at the present time. It is possible that estrogen, by restoring the normal texture of the nasal mucous membranes, protects the telangiectases from trauma and subsequent bleeding. The tendency of the telangiectases to disappear during estrogen therapy might indicate, however, a direct effect on the vascular structure of the lesion itself. Studies are now in progress to determine the mechanism by which these compounds produce the observed effects.

SUMMARY

1. The case histories of five patients with hereditary hemorrhagic telangiectasia who received estrogen or combined estrogen and androgen therapy are described.

2. A decrease in the incidence and severity of epistaxes in all instances was observed.

3. Methods of hormone administration and a description of side-effects and their control are presented.

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CLINICAL VALUE OF SERUM AMYLASE DETERMINATION

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The diagnostic difficulties encountered in disease of the pancreas because of its inaccessibility to physical and roentgenologic examination and lack of simple biochemical tests, such as those used in the detection of diseases of the hepatobiliary tract, are well known. A fairly satisfactory approach to this problem has been the use of tests of pancreatic function.[1] In essence, most tests of pancreatic function deal mainly with the detection of disturbances in pancreatic enzyme concentration in the duodenal contents following hormonal (secretin) stimulation. Such studies have proved invaluable in the detection of pancreatic insufficiency in chronic disease of the pancreas but are of extremely limited value in the patient with acute illness.[2] In practice, the study of impaired external pancreatic function by analysis of duodenal contents is too time consuming, cumbersome, and, most of all, distasteful to the patient.

A fairly simple and informative test of acute pancreatic disease is determination of the amylase and lipase activity of the serum. The diagnostic value of elevated amylase and lipase values has been well established by many investigators.[3] Stocks [3a] was the first to demonstrate the value of the blood amylase level in acute pancreatitis. However, it was not until Elman [3b] reported on his intensive studies that the usefulness and significance of elevated blood amylase levels in acute and subacute pancreatitis gained clinical recognition. Subsequent reports in the literature on the value of serum amylase determinations in relation to diseases of the pancreas have added little to the entity of acute and subacute pancreatitis, but significant contributions have been re-

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2. Dornberger, G. R.; Comfort, M. W.; Wollaeger, E. E., and Power, M. H.: Pancreatic Function as Measured by Analysis of Duodenal Contents Before and After Stimulation with Secretin, Gastroenterology **11**: 701 (Nov.) 1948.

3. (*a*) Stocks, P.: The Quantitative Determination of Amylase in Blood-Serum and Urine as an Aid to Diagnosis, Quart. J. Med. **9**: 216 (April) 1916. (*b*) Elman, R.; Arneson, N., and Graham, E. A.: Value of Blood Amylase Estimations in Diagnosis of Pancreatic Disease: Clinical Study, Arch. Surg. **19**: 943 (Dec.) 1929. Elman, R.: Blood Amylase in Relation to Disease of the Pancreas: Further Observations, Arch. Int. Med. **48**: 828 (Nov.) 1931; The Variations of Blood Amylase during Acute Transient Disease of the Pancreas, Ann. Surg. **105**: 379 (March) 1937. (*c*) Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Transient Acute Pancreatitis, Ann. Surg. **108**: 1029 (Dec.) 1938. (*d*) Lewison, E. F.: Clinical Value of the Serum Amylase Test, Surg., Gynec. & Obst. **72**: 202 (Feb.) 1941. (*e*) McCorkle, H., and Goldman, L.: The Clinical Significance of Serum Amylase Test in Diagnosis of Acute Pancreatitis, Surg., Gynec. & Obst. **74**: 439 (Feb.) 1942. (*f*) Comfort, M. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Lipase and Serum Amylase in the Diagnosis of Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **15**: 427 (July 3) 1940. (*g*) Wapshaw, H.: The Blood Diastase and Lipase Changes in Acute Pancreatitis, Brit. M. J. **2**: 68 (July 10) 1948.

ported on its value in cases of chronic recurrent pancreatitis,[4] carcinoma of the pancreas and of the ampulla of Vater,[5] and gastroduodenal lesions.[6]

The origin of the starch-splitting enzyme amylase found in the blood has been the subject of much dispute. The pancreas secretes amylase not only into the lumen of the duodenum but also into the circulation through the interstitial spaces. This partition of pancreatic enzymes has introduced the concept that the pancreas is an endocrine gland with respect not only to insulin but also to amylase and lipase.[7] How much of the normal amylolytic activity of the serum is due to pancreatic amylase and salivary ptyalin still remains unanswered. However, in pathological states of the pancreas or salivary gland, the increased amylolytic activity of the serum is due to pancreatic amylase or salivary ptyalin.

Experimental studies on animals subjected to total pancreatectomy have demonstrated that the pancreas is not the sole source of blood amylase.[8] Such experimental studies revealed a significant fall in the blood amylase level after total pancreatectomy, followed by a return to a subnormal or normal level.[9] Brunschwig [10] reported a clinical case of total pancreatectomy in which the serum amylase fell to 9 units one week postoperatively and returned to a normal level (71 units) eight weeks postoperatively. It appears unlikely that the salivary gland solely compensates for the loss of the pancreas in maintaining the normal amylase activity of the blood, and undoubtedly other sources in the body contribute to the amylase level. Such sources may be the liver, muscle, and adipose tissue, inasmuch as these organs have been reported to possess amylase activity.[11]

STUDIES ON SERUM AMYLASE VALUES IN VARIOUS CONDITIONS

Serum amylase determinations have proved invaluable in the diagnosis of primary pancreatic disease. It has long been appreciated that serum amylase reflects the existence of a pancreatic lesion but does not reveal the nature of the lesion. However, elevated serum amylase levels, when correlated with clinical findings and additional laboratory studies, frequently establish the nature of the pancreatic lesion. One must also be cognizant of the fact that an elevated serum amylase level is encountered in clinical conditions other than primary disease of the pancreas. This report deals with the elevated amylase levels observed in patients with various conditions, including disease of the pancreas. Also included are serum amylase values obtained in patients with various clinical entities that are believed to be associated with "subnormal" amylase values. The amylase value in this study was determined by the method of Myers.[12] The normal range for serum amylase concentrations in our laboratory is 70 to 240 mg. per 100 cc.

Pancreatic Diseases.—An elevated serum amylase is invariably present in patients with acute pancreatitis, subacute pancreatitis, and chronic recurrent pancreatitis during an acute exacerbation. Neoplasms of the pancreas, namely, those of the head and ampulla of Vater, frequently are associated with elevated serum amylase levels.[5b] Any mechanism that prevents the normal flow of pancreatic juice from the main pancreatic duct into the duodenum may be reflected by an elevation of serum amylase. The mechanisms that cause a partial or complete obstruction of the main pancreatic duct in disease of the pancreas are (1) intramural swellings due to inflammation or tumors of the main duct, and (2) extraluminal pressure on the main duct because of an inflammatory process or tumor in the pancreas. Acute edema may prevent the flow of the amylase from the acinar cells into the ducts and result in elevation of the serum level.[13] Serum amylase activity following permanent ligation of the pancreatic duct in experimental animals has been reported to be transiently increased, with subsequent return to normal,[14] as well as permanently increased.[15] I had the opportunity to study intensively a patient who had undergone resection of the head and uncinate process of the pancreas with permanent ligation of the main pancreatic duct, for carcinoma of the ampulla of Vater. Serum amylase determinations on this patient 18 months and 36 months postoperatively were 923 mg. and 579 mg. per 100 cc., respectively. The maximum serum amylase concentration obtained when last studied (three years postoperatively) was 1,137 mg. per 100 cc. after neostigmine stimulation of the pancreas.[16]

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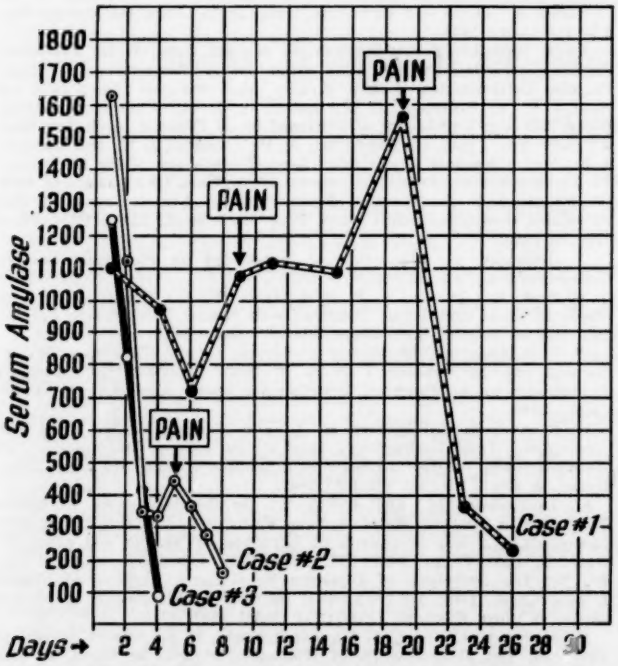
Acute Pancreatitis: It has been reported that in patients with acute pancreatitis, the serum amylase becomes significantly elevated in a matter of hours [3g] and usually reaches its maximum concentration within 48 to 72 hours.[17] In my experience, the amylase reaches a maximum value well over 1,000 mg. per 100 cc. within 12 to 24 hours. My co-workers and I performed sufficient studies on serum amylase activity during the course of acute pancreatitis in 10 recent cases, which proved to be of value in following the clinical course (table 1). Numerous reports have appeared in the literature on the duration of hyperamylasemia following the acute onset of an attack of pancreatitis; and, in general, the consensus is that the serum amylase remains elevated for 24 to 72 hours and then rapidly returns to normal.[18] The duration of hyperamylasemia was 2 to 6 days in seven of our cases and 11 to 24 days in the remaining three cases (table 1). Illustrative cases are graphically shown in the accompanying figure.

TABLE 1.—*Serum Amylase Values in Cases of Acute Pancreatitis*

Case No.	Maximum Serum Amylase Level (Mg./100 Cc.)	Duration of Hyperamylasemia (Days)	Comment
1	1,108	24	Survived
2	1,622	6	Survived
3	1,244	3	Survived
4	1,977	11	Survived
5	2,240	3	Survived
6	1,556	2	Died
7	1,070	3	Died
8	2,520	4	Survived
9	1,389	5	Survived
10	1,790	18	Survived



Serial amylase values in cases of acute pancreatitis.

It has been reported that there is no constant relationship between the height of the serum amylase level and the severity of the attack of acute pancreatitis.[19] My observations are in agreement with this; however, serial determination of the serum amylase concentration has furnished invaluable clinical information as to the activity as well as the duration of the acute process in the pancreas (see accompanying figure).

Chronic Recurrent Pancreatitis: Twenty-five patients with chronic recurrent pancreatitis were studied, and the serum amylase values obtained during an exacerbation are expressed in table 2. Eight of these patients were seen early during the course of their acute painful seizure, and amylase determinations in this group revealed values between 600 and 1,800 mg. per 100 cc. Eleven had subacute exacerbations when seen, with amylase values between 400 and 600 mg. per 100 cc., while six, in whom the acute exacerbation was subsiding on admission to the hospital, had amylase levels in the range of 300 to 400 mg. per 100 cc. The duration of hyperamylasemia in these 25 patients averaged 7 to 10 days; maximum concentrations were seen during the painful period, but elevated amylase levels persisted even after the pain had subsided. The slow return of the serum amylase level to normal in this clinical entity most likely is due to continued activity of the inflammatory process. With progressive destruction of pancreatic tissue resulting from repeated acute exacerbations, the enzyme titer no longer rises with the acute attack, indicating that there is an insufficient number of normal-functioning acinar cells. Three such cases have been collected in our series of chronic recurrent pancreatitis. In these three cases, permanent hyperglycemia, steatorrhea, calcifications in the pancreas, and low to normal serum amylase levels were observed during an acute painful seizure.

TABLE 2.—*Serum Amylase Levels in Twenty-Five Cases of Chronic Recurrent Pancreatitis*

Group A Acute Exacerbation		Group B Subacute Exacerbation		Group C Subsiding *	
Patient	Amylase Level †	Patient	Amylase Level †	Patient	Amylase Level †
S. O.	1,810	M. Z.	552	P. B.	371
S. F.	1,275	F. V.	400	L. S.	349
M. B.	875	M. N.	460	F. S.	305
B. O.	869	O. H.	491	E. W.	397
F. H.	794	S. Q.	478	A. S.	362
F. M.	680	E. D.	440	G. B.	337
M. C.	676	C. B.	412		
T. N.	712	E. B.	467		
		E. W.	459		
		J. K.	405		
		L. G.	481		

* Pancreatitis was subsiding when the patient was admitted to the hospital.
† Milligrams per 100 cc.

Carcinoma of the Pancreas: Determination of the concentration of serum amylase may be of clinical value in the early detection of carcinoma of the pancreas and of the ampulla of Vater.[20] Ross [5b] reported elevated serum amylase levels in one-third of his cases of carcinoma of the head and in 9 out of 10 cases of carcinoma of the ampulla. It is my practice to perform serum amylase determinations on all patients with painful obstructive jaundice suspected of having a pancreatic neoplasm. To date, nine cases of carcinoma of the pancreas and three cases

17. (*a*) Lewison.[3d] McCorkle and Goldman.[3e] (*b*) Warren, K. W.: Acute Pancreatitis, S. Clin. North America **28**: 741 (June) 1948.
18. Lewison.[3d] McCorkle and Goldman.[3e] Heifetz, Probstein, and Gray.[6b] Warren.[17b]
19. Gray, Probstein, and Heifetz.[3c] McCorkle and Goldman.[3e]
20. Comfort and Osterberg.[3f] Ross and Klinge.[5b]

of ampullary carcinoma have been studied. The serum amylase determination was of value in the diagnosis of carcinoma of the head of the pancreas in three out of four cases (table 3). In two cases there was a significant amylase elevation, while in one there was a significant depression of the amylase titer, compatible with extensive atrophy of the acinar cells, which was confirmed by histiological examination. In cases of carcinoma of the body and tail, serum amylase values proved to be of no diagnostic value. In one case of ampullary carcinoma there was an elevated amylase level (case 10, table 3).

TABLE 3.—*Serum Amylase Levels in Cases of Carcinoma of the Pancreas and Ampulla of Vater*

	Case No.	Maximum Serum Amylase Level (Mg./100 Cc.)	Comment
Carcinoma of the head	1	1,426	Jaundiced; surgery confirmed diagnosis
	2	959	Jaundiced; autopsy confirmed diagnosis
	3	147	Jaundiced; lesion localized to head without obstruction of pancreatic duct
	4	82	Jaundiced; inoperable
	5	48	Jaundiced; extensive atrophy of pancreas
Carcinoma of the body or tail	6	115	Not jaundiced; confirmed at surgery (body)
	7	206	Not jaundiced; autopsy revealed lesion of tail
	8	100	Not jaundiced; surgery revealed lesion of body
	9	292	Not jaundiced; autopsy revealed lesion of body
Carcinoma of the ampulla of Vater	10	973	Jaundiced; confirmed at surgery
	11	107	Jaundiced; confirmed at surgery
	12	87	Jaundiced; confirmed at surgery

It appears to me, after studying these 12 cases, that serum amylase determinations may be of some diagnostic value in the early detection of neoplasms of the head of the pancreas and of the ampulla of Vater. However, a normal serum amylase level in a patient with obstructive jaundice contributes nothing to the perplexing problem of differentiating between a benign and a malignant lesion as the basis for the obstruction.

Peptic Ulcer.—The intimate anatomic and physiological relationship of the gastroduodenal tract to the pancreas readily explains the elevated amylase levels that are frequently encountered in cases of penetrating and perforated peptic ulcers. In 1934, Hinton [21] suggested that the study of pancreatic enzymes could be of diagnostic value in cases of duodenal ulcers penetrating into the pancreas. A few years later, Probstein and coworkers [6a] reported four cases of peptic ulcer involving the pancreas in which the blood amylase was found to be moderately elevated. Subsequent reports [22] have established the diagnostic value of elevated amylase values in penetrating peptic ulcers.

My interest in the serum amylase value in cases of penetrating peptic ulcer was stimulated by the need for a simple and reliable test to confirm the clinical impression that a previously uncomplicated duodenal ulcer was penetrating into the pancreas, as strongly suggested by the change in the character of the pain. Since this study was undertaken, nine cases of penetrating peptic ulcer have been collected in which the serum amylase level was found to be elevated. The clinical diagnosis was confirmed at surgery in six of these cases. In a fairly large number of controls (uncomplicated, active peptic ulcer) serum amylase values consistently were found to be within normal limits.

Acute gastroduodenal perforation, without pancreatic involvement, occurring within a few hours after a meal, is frequently associated with an elevated amylase level.[23] This was demonstrated by Pemberton [6c] in his experimental work on dogs. The source of this elevated serum amylase appears to be the pancreatic amylase, which has spilled from the intestine into the peritoneum and reabsorbed into the circulation. My experience with serum amylase values in cases of duodenal perforations is very meager. One such case was studied in which an erroneous diagnosis of acute hemorrhagic pancreatitis was made on the basis of a serum amylase level of 2,000 mg. per 100 cc. Postmortem examination revealed a duodenal perforation with bile peritonitis, with a normal pancreas grossly and microscopically. The common bile duct and pancreatic duct were patent and free from calculi.

Diseases of the Salivary Glands.—It has been conclusively demonstrated that disease of the salivary glands, especially mumps, are associated with elevated serum amylase levels.[24] Such cases rarely present diagnostic problems, and the elevated serum amylase is of interest only because of its source. A few cases of mumps were studied, and in all there were elevated serum amylase levels, ranging from 578 mg. to 950 mg. per 100 cc. These elevations usually reached a maximum concentration by the fourth day of the illness. It was of interest to note that none of the patients with elevated amylase levels had abdominal symptoms.

Renal Disease.—One of the mechanisms that partakes in the "regulation" of the normal amylase level of the serum is renal excretion of amylase. When renal function is impaired, there is retention of amylase in the blood as reflected by elevated values, along with diminished excretion by the kidneys.[25] The level of serum amylase in cases of renal insufficiency seldom reaches the elevations seen in acute pancreatic lesions. My experience in a small number of cases of renal disease with azotemia has shown the serum amylase to be moderately elevated, ranging between 370 and 480 mg. per 100 cc. It was of interest

TABLE 4.—*Serum Amylase Levels in Penetrating Peptic Ulcer*

Patient	Maximum Concentration of Serum Amylase (Mg./100 Cc.)
V. R.	976
W. B.	462
C. M.	540
J. B.	598
D. H.	327
U. G.	543
R. C.	425
J. F.	439
S. M.	300

21. Hinton, J. W.: Chronic Pancreatitis Associated with Peptic Ulcer, Arch. Surg. **28**: 580 (March) 1934.

22. Heifetz, Probstein, and Gray.[6b] Polowe, D.: Blood Amylase, Am. J. Clin. Path. **13**: 288 (June) 1943.

23. Pemberton, Grindlay, and Bollman.[6c] Musgrove.[6d]

24. Dunlop, G. A.: The Diastatic Index in Acute Parotitis, Lancet **2**: 183 (July 22) 1933. Candel, S., and Wheelock, M. C.: Serum Amylase and Serum Lipase in Mumps, Ann. Int. Med. **25**: 88 (July) 1946.

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to note in these cases that as the serum amylase rose there was a parallel rise in the blood urea nitrogen.

Adequate evaluation of moderate elevations of serum amylase requires consideration of the status of renal function. The temporary impairment of renal function frequently encountered in acute hemorrhagic pancreatitis does not alter the significance of the elevated value, for in this acute disease the amylase values are well over 1000 mg. per 100 cc. In cases of chronic renal insufficiency, the serum amylase value usually is under 500 mg. per 100 cc. and rarely poses any problem in the interpretation of this moderate elevation.

TABLE 5.—*Serum Amylase Levels in Cases of Liver Disease*

Patient	Diagnosis	Initial Fasting Serum Amylase Level	Range of Amylase Levels (Serial Determinations)	
			Minimum Concentration	Maximum Concentration
M. M.*	Toxic hepatitis	262	152	254
A. S.	Cirrhosis	158	...	...
A. G.*	Cirrhosis	125	97	132
C. L.	Cirrhosis	130	68	157
P. W.	Fatty infiltration	80	80	276
E. D.*	Hepatitis	109	81	113
C. F.*	Cirrhosis	94	64	157
A. M.	Fatty infiltration	80	80	110
O. D.	Cirrhosis	145	71	167
H. F.*	Cirrhosis	176	126	150
R. H.*	Cirrhosis	152	145	199
C. M.*	Cirrhosis	256	245	309
L. T.	Cirrhosis	232	184	260

* Jaundiced.

Diseases of the Hepatobiliary Tract.—In view of the varied reports [26] on the significance of serum amylase values in cases of hepatic disease, bile duct calculi, cholecystitis, and cholelithiasis, it seemed desirable to evaluate the diagnostic value of serum amylase determination in such conditions.

Liver Disease: Comfort [27f] found normal values for serum amylase in 22 cases of hepatic disease. Gray and co-workers [26c] reported that impaired hepatic function due to liver disease of various types is usually associated with a subnormal level. It seems difficult to offer a valid explanation for a subnormal amylase level in cases of liver disease, unless severe pancreatic insufficiency, either functional or organic, is concomitantly present.

Thirteen cases of liver disease were studied, and my observations are of interest only in that they confirmed the impression that serum amylase levels are within normal limits in cases of disease of the liver. In all cases there was normal pancreatic function as determined by function tests. The serum amylase values observed in this small series of cases of liver disease are expressed in table 5. The serum amylase levels seen in these cases did not confirm the belief that liver disease is associated with low or subnormal amylase values.

Cholecystic Disease: Cholecystic disease is also considered to be associated with a subnormal or low amylase value. This appears most unlikely; if any deviation from normal is to be found, one would anticipate an elevation in light of the frequent associated cholecystic disease in cases of acute and chronic recurrent pancreatitis. Normal serum amylase values were obtained in four cases of obstructive jaundice due to common duct calculi and in two cases of common duct stricture secondary to surgical intervention. One patient (E. J., table 6) with a common duct calculus had a serum amylase level of 333 mg. per 100 cc.; the pancreas was reported by the surgeon to have a "normal" appearance.

Twenty-eight patients with cholecystic disease had repeated serum amylase determinations while in the hospital for a painful attack. The significant serum amylase values obtained are shown in table 6. The clinical diagnosis was confirmed at surgery in 24 cases and by postmortem examination in one case. Clinical and roentgenologic evidence established the diagnosis in the remaining three cases. Serum amylase values in all but one case (E. J.), were within normal limits; the lowest value obtained was 64 mg. per 100 cc.

The amylase values obtained in these 28 cases do not reflect any tendency toward "subnormal" values as is generally believed to be found in cholecystic diseases. However, I am of the opinion that serum amylase determinations in patients with known cholecystic disease and repeated episodes of acute painful seizures may be of diagnostic value in the detection of recurrent pancreatitis. Frequently, the diagnosis of chronic recurrent pancreatitis is missed, and in these cases the condition is usually mistaken for some form of biliary tract disease.

TABLE 6.—*Serum Amylase Values in Cases of Cholecystic Disease*

Chronic Cholecystitis with Cholelithiasis		Chronic Cholecystitis with Common Duct Calculi		Chronic Cholecystitis Without Calculi	
Patient	Amylase Level*	Patient	Amylase Level*	Patient	Amylase Level*
S. N.	202	A. B.	133	O. B.	129
F. J.	144	L. M.	260	D. P.	211
F. R.	160	O. F.	68	H. S.	115
C. G.	255	E. J.	333		
M. S.	120	M. W.	110		
E. K.	190				
D. K.	64				
D. M.	89				
M. I.	195				
C. F.	140				
V. F.	152				
V. C.	102				
C. A.	156				
R. H.	150				
M. C.	102				
L. S.	99				
N. S.	112				
M. J.	191				
M. B.	206				
M. C.	159				

* Milligrams per 100 cc.

Recently, an interesting observation was reported by Gross and co-workers,[27] on a small series of patients with biliary dyskinesia. They noted an elevation in the serum amylase level after the administration of opiates

26. (*a*) Comfort and Osterberg.[27f] Heifetz, Probstein, and Gray.[26b] (*b*) Somogyi, M.: Blood Diastase as an Indicator of Liver Function, Proc. Soc. Exper. Biol. & Med. **32**: 538 (Dec.) 1934; Diastatic Activity of Human Blood, Arch. Int. Med. **67**: 665 (March) 1941. (*c*) Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Clinical Studies on Blood Diastase: Low Blood Diastase as an Index of Impaired Hepatic Function, Arch. Int. Med. **67**: 805 (April) 1941. (*d*) Branch, C. D., and Zollinger, R.: The Value of Blood Diastase in the Diagnosis of Common Duct Stone, Am. J. Surg. **41**: 233 (Aug.) 1938.

27. Gross, J. B.; Comfort, M. W.; Mathieson, D. R., and Power, M. H.: Elevated Values for Serum Amylase and Lipase Following the Administration of Opiates: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **26**: 81 (Feb. 28) 1951.

to such patients. The mechanism for this is the resulting spasm of the sphincter of Oddi induced by administration of morphine or codeine.[27] I have had no opportunity to study the serum amylase response in patients with biliary dyskinesia, but I have seen one patient with biliary tract disease in which spasm of the sphincter of Oddi apparently was induced by meperidine (demerol®) hydrochloride resulting in a significant rise in serum amylase (714 mg. per 100 cc.). When meperidine was not given, subsequent serum amylase values remained within normal limits. At this hospital, we do not administer morphine and allied compounds to patients undergoing serum amylase determinations, especially to those patients with abdominal pain and suspected biliary tract and/or pancreatic disease.

SUMMARY AND CONCLUSIONS

The usefulness and importance of serum amylase determination in acute pancreatic lesions has had clinical recognition since Elman's tremendous contribution to this field. Despite the diagnostic value of serum amylase in pancreatic disease, this simple informative test is frequently not utilized.

Significant elevations of serum amylase occur within a matter of hours in cases of acute pancreatitis, and maximum concentrations are observed within 12 to 24 hours. There appears to be no constant relationship between the height of the amylase level and the severity of the attack; however, it appears that serial serum amylase determinations furnish invaluable information as to the activity and duration of the acute process in the pancreas. The serum amylase test has proved to be invaluable in cases of chronic recurrent pancreatitis. Twenty-five cases of chronic recurrent pancreatitis with hyperamylasemia during an acute exacerbation were collected and are reported in this communication.

The diagnostic value of the serum amylase test in cases of carcinoma of the pancreas and ampulla of Vater was determined in a small series. It was found to be of some value in cases of carcinoma of the head and of the ampulla. In cases of carcinoma of the body and tail, serum amylase levels were of normal value, as one would anticipate in view of their location and the uninvolvement of the main pancreatic duct.

Certain types of gastroduodenal lesions are associated with elevated serum amylase levels, especially in cases of duodenal perforations without pancreatic involvement. One such case was studied and is herein reported. Penetrating peptic ulcers frequently involve the pancreas and are readily diagnosed clinically on the basis of the moderate elevations in serum amylase. Nine such cases were collected and are included in this report. Other clinical conditions associated with elevated serum amylase values are diseases of the salivary glands and renal insufficiency. From the observation of elevated serum amylase levels in these conditions one readily realizes that elevated amylase values are not pathognomonic of primary pancreatic disease. However, critical evaluation of the clinical findings, along with the height of amylase elevation, will enhance the usefulness of the serum amylase test and not detract from its diagnostic value.

The previous belief that liver disease and cholecystic disease are associated with "low" or "subnormal" serum amylase levels could not be confirmed. Serum amylase determinations in the cases herein reported almost consistently revealed values within normal limits.

I am of the opinion that significant elevations reflect a pathological increase of either pancreatic amylase or salivary ptyalin because of disease of the pancreas or salivary gland. The elevated values encountered in cases of various abdominal conditions other than primary pancreatic disease are indicative of associated or secondary pancreatitis or excessive absorption of the "exocrine" pancreatic amylase, such as occurs in duodenal perforations. The slight to moderate elevations encountered in cases of renal insufficiency are readily understood.

Serum amylase determinations routinely should be made in all patients with acute abdominal pain. Elevated values in such patients invariably are of diagnostic value when correlated with other clinical findings. Critical evaluation of an elevated serum amylase enhances the diagnostic value of this test.

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CHROMIUM INTOXICATION

WITH SPECIAL REFERENCE TO HEPATIC INJURY

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Although chromium compounds have been known for many years to be toxic to various organs of the body, primary hepatic injury has not been a conspicuous clinical finding. The organs most frequently injured by these agents appear to be those that come in direct contact with them, either by external exposure or by excretion, namely, the skin, the mucous membranes, and the kidneys.

A variety of surface lesions have been ascribed to contact with soluble chromium compounds. As early as 1827, Cumin [1] described the characteristic "chrome hole" lesions. These occur on exposed parts of the skin, especially the hands, and are punched out, deeply penetrating, painless ulcers.[2] Macular erythema, scarlatinoid

Dr. C. D. Proctor performed the polarographic determinations of chromium in the urine specimens.

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1. Cumin, W.: Remarks on the Medicinal Properties of Madar, and on the Effects of Bichromate of Potass on the Human Body, Edinburgh M. J. 28: 295-302, 1827

and pustular eruptions, and eczematoid lesions of the skin due to contact with these substances have also been reported.[3] Ulceration and perforation of the nasal septum due to inhalation of plating solution fumes have been described frequently.[4] There is little surrounding mucosal inflammation, but there may be pronounced hyperemia. Painless inflammation of the oral mucous membranes, perforating ulcers of the palate, and ulcers of the eyelids, conjunctiva, and cornea also occur.[5] Inhalation of chromium compounds has been implicated in the pathogenesis of certain cases of pneumoconiosis, allergic asthma, and respiratory tract carcinoma.[6] Inflammation of the respiratory tree has been produced in animals by inhalation of chromic acid dust.[7]

Ingestion of chromium compounds, usually potassium bichromate, leads to severe vomiting, thus preventing much absorption. Nevertheless, instances of systemic poisoning due to absorption of chromium from the gastrointestinal tract and even from the skin have been reported in humans and produced in experimental animals.[8] Once absorbed, the compounds are eliminated by the kidneys primarily and in the bile and feces. Experimentally, it has been shown that 60% of a single dose of chromium is eliminated in the urine within the first eight hours.[8g] This would account for the frequency of uremia in cases of acute poisoning.[9] In humans the tubules are the primary site of injury, whereas in animals glomerular as well as tubular damage has been produced.[10] Other regions reported to be injured by chromium are the central nervous and hematopoietic systems.[11] Hepatic abnormalities have been reported only occasionally, for the most part in accidental human poisonings due to unusual exposure to chromates or in the experimental intoxication of animals. Hepatomegaly without jaundice was noted in a person poisoned acutely, and fatty livers have been found at autopsy in cases of acute and chronic intoxication.[12] An experimental study of chronic chromium poisoning in rabbits demonstrated liver cell degeneration, inflammatory cell infiltration, Kupffer cell proliferation, and large amounts of chromium in the liver.[8g]

The existence of hepatic injury due to the usual industrial exposure to chromium has not been recognized. Surveys of persons in contact with these compounds, for example, in the electroplating, aircraft, and shipbuilding industries, have emphasized the skin and mucous membrane lesions but have not found clinical evidence of systemic poisoning.[13] Blair [4g] stated, "There is no evidence, from the literature or otherwise, that any injury from contact with chromic acid solution or spray in chromium plating develops into a constitutional disease."

We recently had the occasion to study an employee of a chromium plating plant, who had been admitted to the Cook County Hospital because of jaundice. Urinary chromium excretion was found, and the results of hepatic tests and findings on liver biopsy were compatible with the diagnosis of acute hepatitis. In an attempt to determine whether there is a relation between industrial exposure to chromium and liver injury, eight fellow workers were screened; in four, significant urinary chromium excretion was found. The four were studied by a series of hepatic tests and, but for one, by needle biopsy of the liver. Because of the widespread industrial use of chromium at present, these cases are reported to call attention to the possibility of liver injury due to subtle intoxication with these compounds.

METHODS

Twenty-four hour urine specimens were digested with nitric and sulfuric acids and evaporated to dryness. The residue was quantitatively analyzed for chromium, as chromate, by polarography.[14] The hepatic tests performed are listed in tables 1 and 3. Liver biopsy was performed by use of the Vim-Silverman needle. The tissue was fixed in formaldehyde solution, and sections were stained with hematoxylin-eosin, aniline blue, trichrome, iron, hemofuchsin, and silver stains.

REPORT OF CASES

CASE 1.—A. J., a 36-year-old Negro woman, was admitted to Cook County Hospital on Feb. 9, 1951. She had been employed in a chromium plating factory continuously for five years, working next to a chromic acid bath. For the past year she experienced intermittent abdominal swelling. Three weeks prior to admission, she noted pruritus and anorexia, which became increasingly severe. Two weeks later icterus appeared, and the stools became lighter and the urine darker in color. These symptoms persisted until admission. There was no history of alcoholism or exposure to other known toxins.

She was well developed physically, in no apparent discomfort, and afebrile. The skin was excoriated mildly, especially over the back. The scleras were moderately icteric. A few lymph nodes were palpable in the neck, axillas, and groin. The nasal mucosa was intact. The lungs and cardiovascular system were normal. The level of the abdomen was 2 cm. above the xiphopubic line. Neither liver nor spleen was palpable, and ascites was not demonstrable.

Urinalysis revealed a specific gravity of 1.025, no albumin or sugar, 2+ bilirubin, and 2+ urobilinogen. Within two days bilirubin was absent from the urine and urobilinogen excretion increased to 4+; by the 16th day, the latter had returned to nor-

2. (*a*) White, R. P.: The Dermatergoses: or Occupational Affectations of the Skin, ed. 4, London, H. K. Lewis & Co., 1934, p. 190. (*b*) Schwartz, L.: Skin Hazards in American Industry: Part III, Public Health Bulletin 249, United States Treasury Department, Public Health Service, 1939, pp. 42-47. (*c*) Da Costa, J. C.; Jones, J. F. X., and Rosenberger, R. C.: Tanner's Ulcer, Chrome Sores, Chrome Holes, Acid Bites, Ann. Surg. **63**: 155-166 (Feb.) 1916.

3. (*a*) Cumin.[1] (*b*) Ellis, E. A.: Occupational Dermatoses in Aircraft Workers: Chromate Dermatitis, Occup. Med. **2**: 452-462 (Nov.) 1946. (*c*) Hall, A. F.: Occupational Contact Dermatitis among Aircraft Workers, J. A. M. A. **125**: 179-185 (May 20) 1944. (*d*) Harris, M. C.: Contact Dermatitis due to Contact with Chrome 17% Steel Identification Tags of the United States Navy, J. Allergy **16**: 299-301 (Nov.) 1945. (*e*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939. (*f*) Urban; Colden, C.; Hanser, R., and Forschbach: Ueber Chromatvergiftungen, Klin. Wchnschr. **56**: 363-370 (April 21) 1919.

4. (*a*) Zvaifler, N.: Chromic Acid Poisoning Resulting from Inhalation of Mist Developed from 5% Chromic Acid Solution: I. Medical Aspects of Chromic Acid Poisoning, J. Indust. Hyg. & Toxicol. **26**: 124-126 (April) 1944. (*b*) Dixon, F. W.: Perforations of the Nasal Septum in Chromium Workers: Report of 18 Cases, J. A. M. A. **93**: 837-838 (Sept. 14) 1929. (*c*) Legge, T. M.: The Lesions Resulting from the Manufacture and Uses of Potassium and Sodium Biochromate, in Oliver, T.: Dangerous Trades, New York, E. P. Dutton & Co., Inc., 1902, pp. 447-454. (*d*) Watson-Williams, E.: Chrome Ulceration of the Nose, Practitioner **140**: 619-624 (May) 1938. (*e*) Bloomfield, J. J., and Blum, W.: Health Hazards in Chromium Plating, Pub. Health Rep. **43**: 2330-2351 (Sept. 7) 1928. (*f*) Lieberman, H.: Chrome Ulcerations of the Nose and Throat, New England J. Med. **225**: 132-133 (July 24) 1941. (*g*) Blair, J.: Health Hazards in Chromium Plating, Ohio State M. J. **27**: 142-145 (Feb.) 1931.

5. Schwartz.[3b] Sutton and Sutton.[3e]

6. (*a*) Letterer, E.; Neidhardt, K., and Klett, H.: Chromatlungenkrebs und Chromatstaublunge, Arch. f. Gewerbepath. u. Gewerbehyg. **12**: 323-361 (Sept.) 1944. (b) Lukanin, W. P.: Zur Pathologie der Chromat-Pneumokoniose, Arch. f. Hyg. **104**: 166-174, 1930. (c) Joules, H.: Asthma from Sensitisation to Chromium, Lancet **2**: 182-183 (July 23) 1932. (*d*) Machle, W., and Gregorius, F.: Cancer of the Respiratory System in the United States Chromate-Producing Industry, Pub. Health Rep. **63**: 1114-1127 (Aug. 27) 1948.

7. Galloro, S.: Experimental Investigation on Occupational Chromium Poisoning in the Electro-Chromium Plating Industry, Folia med. **24**: 1256-1265 (Nov. 30) 1938; abstracted, J. Indust. Hyg. & Toxicol. **21**: 98 (April) 1939.

mal. The hemogram showed 80% hemoglobin, 4,210,000 red blood cells per cubic millimeter, 6,100 white blood cells per cubic millimeter, 76% polymorphonuclear leukocytes, 1% eosinophils, 14% lymphocytes, 9% monocytes, and a few target cells. The blood Wassermann reaction was negative. The chest x-ray was normal.

TABLE 1.—*Results of Hepatic Tests in Case 1*

Test *	2/12/51	2/19/51	2/26/51	3/6/51	3/19/51
Icterus index (4-6 units)	95	25	12	28	17
Cephalin cholesterol flocculation (0-1+)	2+	4+	2+	0	0
Thymol turbidity (1.0-4.0 units)	20.8	9.4	6.3	6.8	5.4
Total protein (6.5-8.0 gm./100 ml.)	7.2	7.6	6.7	7.0	8.2
Albumin (4.0-5.5 gm./100 ml.)	4.0	5.2	..	5.0	5.2
Globulin (1.5-3.4 gm./100 ml.)	3.2	2.5	..	2.0	3.0
Gamma globulin † (0.6-1.25 gm./100 ml.)	1.89	2.02	1.85	1.4	1.57
Total cholesterol (150-250 mg./100 ml.)	258	270	262	205	265
Cholesterol ester/total cholesterol 0.50-0.75	..	..	0.41	..	..
Alkaline phosphatase (1.5-4.0 Bodansky units)	4.8	3.8	2.0	3.1	1.9
Inorganic phosphorus (3.0-5.0 mg./100 ml.)	4.0	3.4	3.2	4.1	3.5
Nonprotein nitrogen (20-40 mg./100 ml.)	30	30	..	..	..
Sulfobromophthalein retention, 2 mg./kg. dose (0-6%)	..	..	..	..	30

* Normal values in our laboratory are given in parentheses.
† de la Huerga, J., and Popper, H.: Estimation of Serum Gamma Globulin Concentration by Turbidimetry, J. Lab. & Clin. Med. **35**: 459-465 (March) 1950.

The hospital course was one of gradual improvement, with disappearance of visible icterus in 16 days. Twice the patient had episodes of abdominal distention, vague abdominal discomfort, and headache, which lasted 24 to 48 hours and subsided without therapy other than analgesics. X-ray of the abdomen showed moderate amounts of gas in the large bowel during these episodes. Initial gastrointestinal x-rays showed findings suggestive of irritable colon, which later disappeared. The gallbladder was normal.

The results of the hepatic tests are tabulated in table 1. Initially the icterus index was 95 units, the thymol turbidity 20.8 units, and the cephalin-cholesterol flocculation 2+ (later 4+). Serum globulin, especially the gamma fraction, was moderately elevated. Serial determinations showed gradual return toward normal. Five weeks after admission sulfobromophthalein retention was 30%. Qualitative examination of the 24-hour urine on the fourth hospital day was strongly positive for chromium. Subsequent quantitative analyses of 24-hour urine specimens, before and after the use of dimercaprol injection, are recorded in table 2.

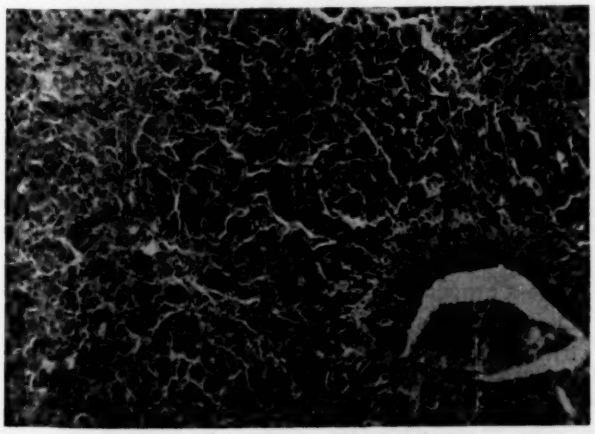


Fig. 1 (case 1).—There is marked centrolobular necrosis and Kupffer cell proliferation. The enlarged portal field is infiltrated with lymphoid and histiocytic cells and shows moderate bile duct proliferation. (× 120)

Biopsy of the liver was performed on the eighth hospital day. Histologically, there was necrosis of the liver cells of the central zone with dilatation of the sinusoids. The few liver cells preserved in the zone had eosinophilic cytoplasm, and the nuclei were markedly pyknotic or absent. The Kupffer cells were increased in number and size. There were focal accumulations of lymphoid type cells within the sinusoids or in place of liver cells. Bile pigment was noted chiefly in liver cells in the central zone, but occasionally elsewhere. The portal fields were moderately enlarged and showed lymphocytic and histiocytic infiltration and a moderate degree of mature bile duct and capillary proliferation. No fat was seen (fig. 1 and 2).

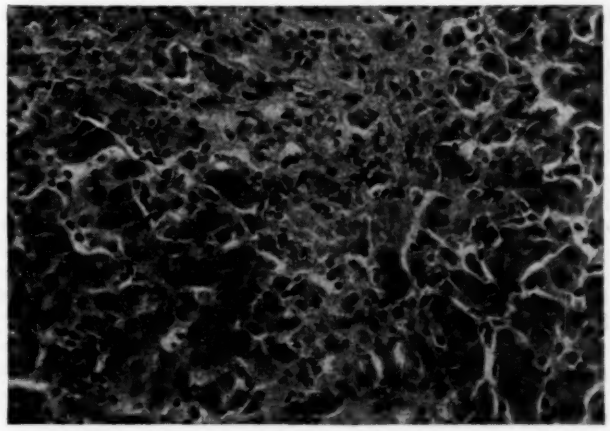


Fig. 2 (case 1).—There is necrosis of the liver cells in the center of the lobule. The cells that remain show variation in size and in nuclear and cytoplasmic staining. Marked proliferation of Kupffer cells and focal accumulations of lymphoid and histiocytic cells can be seen. (× 240)

TABLE 2.—*Amount of Chromium Recovered in Urine of Five Chromium Workers*

Case No.	Date	Chromium in Urine, Mg./24 Hr.
1	2/13/51	++++ ‡
	2/24/51	0.000
	3/14/51	0.739
	3/18/51	1.480
	3/19/51 *	0.630
	3/20/51 †	0.135
2	3/ 4/51	2.880
3	3/ 4/51	2.840
	3/18/51	0.186
4	3/ 4/51	0.495
5	3/ 4/51	0.184

* The patient received 300 mg. of dimercaprol injection intramuscularly during collection of this specimen.
† The patient received 200 mg. of dimercaprol injection intramuscularly during collection of this specimen.
‡ Qualitative only.

8. (*a*) Philipson: A Case of Poisoning by Bichromate of Potash, Lancet **1**: 138-139 (Jan. 16) 1892. (*b*) Brieger, H.: Zur Klinik der akuten Chromatvergiftung, Ztschr. f. exper. Path. u. Therap. **21**: 393-408 (Nov.) 1920. (*c*) Major, R. H.: Case of Chromic Acid Nephritis, Bull. Johns Hopkins Hosp. **33**: 56-61 (Feb.) 1922. (*d*) Goldman, M., and Karotkin, R. H.: Acute Potassium Bichromate Poisoning, Am. J. M. Sc. **189**: 400-403 (March) 1935. (*e*) Sander, J. F., and Camp, C. D.: Chromium Poisoning in Infancy, ibid. **198**: 551-554 (Oct.) 1939. (*f*) Lewin, L.: Ueber die gewerbliche Vergiftung mit Chromverbindungen, Ztschr. f. Gewerbehyg. **15**: 159-162, 1908. (*g*) Bianchi, G.: Sulla intossicazione da cromo, Turin, Attualita di Scienze Mediche, 1941, p. 48.

9. Brieger.[8b] Major.[8c] Goldman and Karotkin.[8d]

10. Galloro.[7] Brieger.[8b] Hunter, W. C., and Roberts, J. M.: Experimental Study of the Effects of Potassium Bichromate on the Monkey's Kidney, Am. J. Path. **9**: 133-148 (Jan.) 1933. Hasegawa, M.: Studies on the Detoxicating Hormone of the Liver (Yakriton): Effect of Yakriton upon Chromic Nephritis, Tohoku J. Exper. Med. **32**: 163-176 (Jan. 30) 1938. Ohta, F.: Studies on the Detoxicating Hormone of the Liver (Yakriton): Contribution to the Usage of Yakriton against Experimental Chromate Nephritis, ibid. **39**: 37-46 (Sept. 30) 1940.

11. Brieger.[8b] Sander and Camp.[8e] Bianchi.[8g]

12. Letterer, Neidhardt, and Klett.[6a] Brieger.[8b] Goldman and Karotkin.[8d] McNally, W. D.: Toxicology, Chicago, Industrial Medicine, 1937.

13. Hall.[3c] Zvaifler.[4a] Bloomfield and Blum.[4e] Blair.[4g] Vaccaro, L.: Chromium Poisoning, Indust. Med. **10**: 246-247 (June) 1941. Brown, E. W.: Health Hazards from Lead Paint and Zinc Chromate Paint: Incidence in Modern Construction, Maintenance and Scrapping of Ships, Occup. Med. **5**: 739-758 (June) 1948.

14. Proctor, C. D.: To be published.

CASE 2.—J. R., a 28-year-old Negro, worked next to a chromium plating tank for four years. For the past year he noticed a metallic taste in his mouth. Six months previously nasal ulcers developed, which were successfully treated with petrolatum applications. There was no history of alcoholism or exposure to other known toxins. Abnormal physical findings included injection of the nasal and pharyngeal mucosa and tenderness over the area of liver dulness. Urinalysis, hemogram, chest x-ray, and gallbladder visualization gave normal results. The results of the hepatic tests and quantitative analyses of the urine for chromium are recorded in tables 2 and 3. Prior to liver biopsy, the prothrombin activity was 65% of normal. After 40 mg. of synthetic vitamin K was given parenterally, no significant change in prothrombin activity occurred.

Microscopically, the liver cells around the central vein contained pyknotic nuclei and a smudgy, or homogeneous, eosinophilic cytoplasm. Elsewhere, the nuclei showed moderate pleomorphism, and the cytoplasm contained fat and hydropic vacuoles. A moderate amount of bile pigment was found in the liver cells. The Kupffer cells were slightly increased in number, and scattered focal necroses were seen. The portal fields were enlarged and very cellular, and moderate capillary, bile duct, and fibroblast proliferations were noted (fig. 3).

CASE 3.—A. L. J., a 31-year-old Negro, worked in the chromium plating industry for four years. For the past two years he periodically noted soreness and redness of the nasal mucosa and had muscular aches. There was no history of alcoholism or exposure to other known toxins. There was injection of the nasal mucosa. The results of the remainder of the physical examination, as well as the urinalysis, hemogram, chest x-ray, and barium enema, were normal. The results of the hepatic tests and quantitative examination of the urine for chromium are recorded in tables 2 and 3. In the section a few of the liver cells about the central vein contained fine, granular bile pigment, and an occasional focal necrosis was noted. Otherwise, the liver was normal.

CASE 4.—C. R., a 27-year-old Negro, worked in a chromium plant for one year, periodically at the chromic acid bath. He had an epistaxis one month before examination but was otherwise symptom free. Except for hyperemia of the nasal mucosa, physical findings were normal. The results of urinalysis, hemogram, chest x-ray, and gallbladder visualization were normal. The results of the hepatic tests and the quantitative examination of the urine for chromium are recorded in tables 2 and 3.

Morphologically, the cells immediately around the central veins showed smudginess and eosinophilia of the cytoplasm, pyknotic nuclei, and occasional karyorrhexis. The Kupffer cells were increased in number and often increased in size. There were foci of lymphocytes within the sinusoids and occasionally in place of liver cells. The portal fields were small and contained a slight amount of lymphocytic infiltration. A few liver cells contained granular or diffuse bile pigment.

CASE 5.—R. E. J., a 22-year-old Negro was removed from the plating to the mechanic section after six months of employment because of the development of nasal ulcers. He had no subsequent symptoms. The results of the hepatic tests and analyses of the urine are recorded in tables 2 and 3. Liver biopsy was not done in this case.

COMMENT

Because of their protein-precipitating and oxidizing properties, chromium trioxide, chromates, and bichromates are potent protoplasmic poisons. Chromic oxide, trivalent chromium salts, and metallic chromium are much less toxic.[15] Chromium has been reported to be present in the teeth but has not been found in other tissues normally.[16] In intoxications, however, it has been found widely distributed in most organs and secretions, and its appearance in the urine has been reported in several patients.[17] Exposure to these substances is common, because of their widespread use in industries such as printing, tanning, photography, dyeing, and electroplating.[18] In the last process, the metal to be plated with chromium is immersed in a solution of chromic acid, through which is passed an electric current. Owing to the liberation of oxygen and hydrogen gases at the electrodes, a fine spray of chromic acid arises over the bath, carrying chromium trioxide into the air. The maximum safe concentration of chromium trioxide has been considered to be 0.1 mg. per cubic meter of inhaled air. Unless proper ventilation is present, the mist from chromic acid baths may lead to concentration of chromium trioxide of 2.5 to 6.5 mg. per cubic meter of air.[4e]

All our patients worked in a chromium plating plant for one to five years, four of the five patients constantly next to the chromic acid bath. Four had a history or findings, or both, of the commonest type of injury in the chromium plating industry, namely, nasal hyperemia or ulceration. All were eliminating significant amounts of chromium when examined. Two showed clinical evidence of hepatic involvement: A. J. (case 1) was jaun-

TABLE 3.—*Results of Hepatic Tests, Cases 2 to 5*

Test *	Case 2		Case 3		Case 4		Case 5,
	3/7/51	3/19/51	3/7/51	3/22/51	3/7/51	3/27/51	3/7/51
Icterus index (units)	9	6	11	19	6	11	6
Cephalin cholesterol flocculation	0	0	0	0	0	0	0
Thymol turbidity (units)	2.3	3.0	5.2	6.3	4.2	3.2	3.0
Total protein (gm./100 ml.)	7.0	7.6	6.7	7.2	7.9	8.1	7.2
Albumin (gm./100 ml.)	4.1	4.7	4.0	4.9	4.8	4.6	4.4
Globulin (gm./100 ml.)	2.9	2.9	2.7	2.3	3.1	3.5	2.8
Gamma globulin † (gm./100 ml.)	1.05	1.40	1.26	1.40	1.24	1.14	0.97
Total cholesterol (mg./100 ml.)	200	205	200	205	150	160	178
Cholesterol ester/total cholesterol	..	..	0.42	..	..	..	..
Alkaline phosphatase (Bodansky units)	2.4	1.8	2.4	1.9	2.0	..	2.6
Inorganic phosphorus (mg./100 ml.)	3.0	3.0	3.4	3.5	4.2	..	3.8
Sulfobromophthalein retention (%)	15.7	..	24.0	25.3	9.0	0.0	8.0

* For normal values in our laboratory, see table 1.
† de la Huerga and Popper (see reference in table 1).

15. (*a*) Heyroth, F. F.: The Metals (Except Lead), in Patty, F. A.: Industrial Hygiene and Toxicology, New York, Interscience Publishers, Inc., 1949, vol. 2, pp. 675-738. (*b*) Akatsuka, K., and Fairhall, L. T.: The Toxicology of Chromium, J. Indust. Hyg. **16**: 1-24 (Jan.) 1934. (*c*) Conn, L. W.; Webster, H. L., and Johnson, A. H.: Chromium Toxicology: Absorption of Chromium by the Rat When Milk Containing Chromium Was Fed, Am. J. Hyg. **15**: 760-765 (May) 1932.

16. Heyroth.[15a] Lowater, F., and Murray, M. M.: Chemical Composition of Teeth: V. Spectrographic Analysis, Biochem. J. **31**: 837-841 (May) 1937.

17. Letterer, Neidhardt, and Klett.[6a] Brieger.[8b] Goldman and Karotkin.[8d] Bianchi.[8e] Chromium Nephritis and Detection in Urine, Queries and Minor Notes, J. A. M. A. **110**: 1060 (March 26) 1938.

18. Chromium Poisoning: Cause and Prevention, Industrial Health Series, No. 5, United States Department of Labor, 1943.

diced, and J. R. (case 2) had definite hepatic tenderness but was otherwise well. The other patients had no physical evidence of systemic disease.

Each patient had abnormalities in the results of the hepatic tests. A. J., whose clinical course was one of hepatitis, had grossly abnormal results of hepatic tests initially, followed by gradual improvement. The liver biopsy showed centrolobular necrosis, marked Kupffer cell proliferation, enlarged portal fields with lymphocytic and histiocytic infiltration, and bile duct proliferation. J. R., having liver tenderness on physical examination, had diminished prothrombin activity, which did not respond to adequate parenteral administration of vitamin K; a borderline elevation of the icterus index; and abnormal retention of sulfobromophthalein. Here, the findings on biopsy were focal necroses, moderately increased cellularity of the portal spaces, moderate damage of the cells around the central veins, and bile pigment imbibition. A. L. J. (case 3) had an elevated icterus index, reduced cholesterol ester percentage, and abnormal retention of sulfobromophthalein. In this instance the only abnormal finding on microscopic examination of the liver was the finely granular bile pigment imbibition. C. R. (case 4) had an elevated icterus index on one occasion (normal on another), elevated serum globulins, and abnormal retention of sulfobromophthalein. The biopsy showed minimal central degenerative changes combined with bile pigment imbibition. R. E. J. (case 5), most removed from the chromic acid bath and found to be eliminating the least amount of chromium, had borderline retention of sulfobromophthalein as the only abnormal result of the hepatic tests. Biopsy was not done in this case.

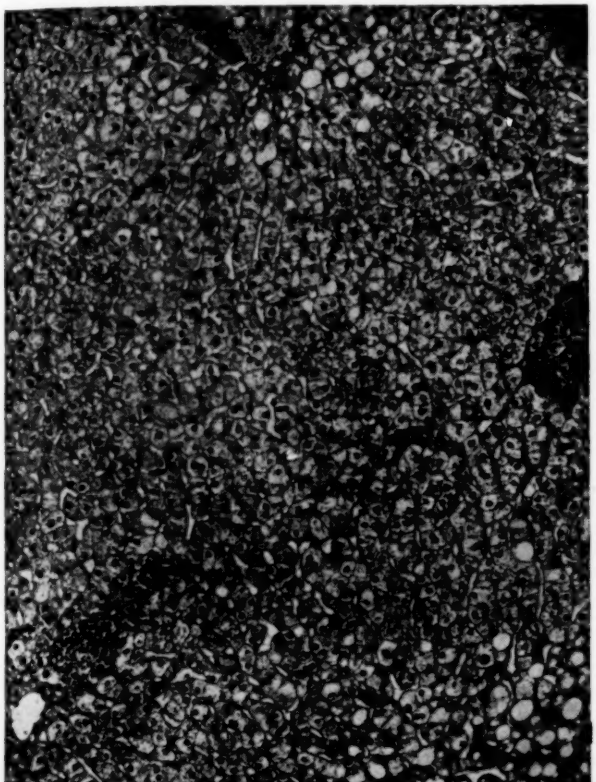


Fig. 3 (case 2).—The cells around the central vein show alterations in nuclear and cytoplasmic staining. Scattered fat and hydropic vacuoles are seen. The portal fields are enlarged and very cellular. (× 125)

Of the four biopsies, two showed pronounced and two slight abnormalities of hepatic structure. The histological changes found in the patient in whom jaundice developed were strikingly similar to those observed in experimental chromium poisoning in rabbits.[8g]

The indictment of chromium in these cases as the causative hepatotoxin seems justified in view of the history of exposure to a toxic form of chromium (chromium trioxide from chromic acid mist), the absence of exposure to other toxins (including alcohol), the finding of chromium in the urine in significant amounts, abnormalities in the results of hepatic tests, and the fact that the pathological findings in the liver did not resemble those seen in viral or other infective hepatitis, but rather those seen in the so-called toxic hepatitis.[19]

If it be true that industrial exposure to the toxic chromium compounds may cause systemic as well as surface injury in the human, the health hazard in plants using these compounds is not as negligible as suggested in the literature. Prophylactic measures, such as adequate ventilation and protective covering, should be taken in all factories to reduce exposure to a minimum. Skin and mucous membrane lesions should be treated promptly to prevent chronic systemic absorption of these compounds.[20] The effect of dimercaprol injection could not be evaluated in our patient because she was recovering at the time it was used.

The clinical well-being of most of our patients despite the presence of hepatic dysfunction as evidenced by hepatic tests and biopsy suggests that similar cases may have been overlooked because of the lack of more recent techniques for hepatic examination. The incidence of systemic poisoning in industries using chromium compounds, therefore, may require further investigation.

SUMMARY

Acute hepatitis with jaundice was observed in a person employed in the chromium electroplating industry. Chromium was identified in the urine on several examinations. Liver biopsy showed histological changes resembling those found in "toxic" hepatitis. In four other electroplating workers, found to be excreting significant amounts of chromium in the urine, hepatic tests and liver biopsy showed mild to moderate abnormalities. These workers had no symptoms related to the liver or other internal organs but did have the nasal lesions frequently attributed to chromium intoxication. The appearance of hepatitis in a chromium worker, as well as the existence of hepatic dysfunction in workers with no constitutional complaints, suggests that subtle systemic intoxication of employees of industries using chromium may be a definite health hazard.

629 S. Wood St.

19. Popper, H., and Franklin, M.: Viral Versus Toxic Hepatic Necrosis, Arch. Path. 46: 338-376 (Oct.) 1948.
20. Zvaifler.[4a] Bloomfield and Blum.[4c] Blair.[4g] Footnote 18.

CLINICAL NOTES

FATAL VENTRICULAR FIBRILLATION FOLLOWING PROCAINE AMIDE HYDROCHLORIDE THERAPY

REPORT OF A CASE

John M. Read, M.D., Elko, Nev.

This is a report of death immediately following an intravenous injection of procaine amide ("pronestyl") hydrochloride. The case is reported because it is felt that instances of important untoward as well as the favorable effects of a drug should be generally known. Except for deaths in moribund patients and/or following exceedingly large, rapidly administered doses [1] no instances of death following the routine, cautious use of procaine amide have come to my attention. Aside from an increasingly cautious tone in the more recent articles [2] and an isolated report of agranulocytosis following oral administration,[3] most authors have mentioned the relative lack of serious toxic effects.[4]

REPORT OF A CASE

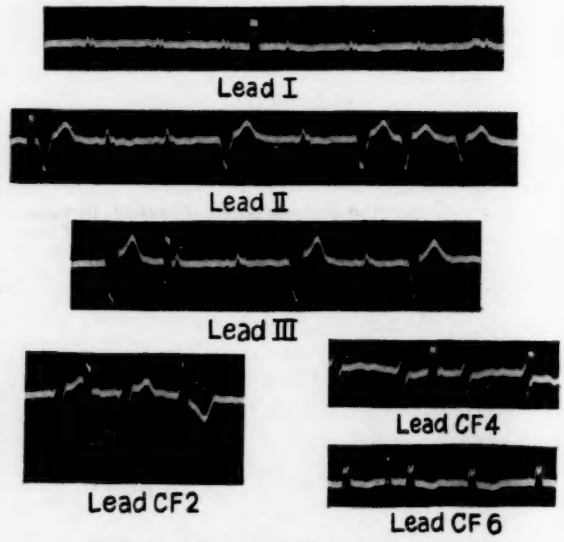
A 61-year-old widow was admitted to the Elko General Hospital in June, 1951, after a third attack of acute weakness and dyspnea in 48 hours. She had had rheumatic fever at 11 years. In 1935 she was admitted to the Elko General Hospital and a diagnosis of mitral stenosis and congestive failure was made. Since then she had been admitted to several hospitals in the Western states and had taken digitalis preparations irregularly. Prior to this recent admission she had taken no digitalis for one week. For the past several years she had noted an irregular "jumpy" heart from time to time but had noted no lasting spells.

On admission she appeared tired. The temperature and respirations were normal. A slight, but definite, malar flush was present. The ocular fundi were normal, and the neck veins not distended. The lungs showed only a few scattered rales at both bases posteriorly. The apex beat was palpable in the sixth intercostal space at the anterior axillary line, and the area of cardiac dulness corresponded to this. The second pulmonic sound was accentuated, and the loud apical first sound was preceded by a rumbing murmur. A harsh, grade 3 systolic murmur was heard over the precordium. The blood pressure was 120/80. An occasional premature beat was heard. A slightly tender, smooth liver edge descended 3 cm. below the right costal margin. There was ankle edema present, graded as 1+. There was no sacral edema.

The blood cell count, urine, sedimentation rate, and stool were normal. The result of the test with VDRL antigen was negative. The chest roentgenogram showed hazy, diffuse densities extending from both hili and a greatly enlarged heart with a typical "mitral" configuration. The electrocardiogram showed slurred ventricular complexes and diphasic T waves in the limb leads. The QRS time was 0.14 seconds. The R-T segment was slightly elevated in CF_1, CF_2, and CF_3 and slightly depressed with inverted or diphasic T waves in CF_4, CF_5, and CF_6. Successive, rapid premature beats, apparently arising in the right ventricle, were present (see the accompanying figure).

On the second day the patient complained of a smothering feeling, palpitation, and heaviness in the chest. That evening the nurse noted the pulse rate to be 130 and called the patient's physician. When seen at 11:30 p. m., she was apprehensive, cold, and orthopneic. She complained of palpitation, which she believed to have been present since 9 a. m. (14 hours). The neck veins were engorged. The apical and radial rates were equal and varied between 162 and 164. There was marked variation in the intensity of the first sound as heard over the apex and precordium, but the rhythm seemed regular. The blood pressure was 110/74. Carotid sinus pressure was not applied.

In the light of the bedside findings and the recent electrocardiographic observations, it was felt that ventricular tachycardia was present. Because of the patient's condition, prompt



Electrocardiogram taken 36 hours before death.

treatment seemed imperative. Accordingly 200 mg. (2 cc.) of procaine amide hydrochloride was given slowly into the left antecubital vein. The injection required three minutes, and a stethescope was held in place over the precordium during and after the injection. The rate and rhythm remained unchanged until just after the needle was withdrawn, when, for a few cycles, the rhythm became irregular; then the rate abruptly rose and no count could be made. At this time the patient uttered a faint cry and ceased breathing for a moment. The heart continued to beat wildly and very rapidly for 15 to 20 seconds; then the intensity of the heart sounds diminished and became inaudible. Slow, irregular respirations continued for two and a half minutes after the cessation of heart sounds.

COMMENT

The close temporal relationship between the administration of the drug and sudden death was so striking as to exclude the possibility of coincidental death from an inevitable ventricular fibrillation. Though electrocardiographic and blood pressure controls were lacking, there seems little doubt that death was due to ventricular fibrillation. The remainder of the bottle was sent to the manufacturer's laboratory; the contents were reported as procaine amide hydrochloride without impurities.

From the Elko Clinic.

1. (*a*) Kayden, H. J.; Steele, J. M.; Mark, L. C., and Brodie, B. B.: Use of Procaine Amide in Cardiac Arrhythmias, Circulation **4**: 13 (July) 1951. (*b*) Berry, K.; Garlett, E. L.; Bellet, S., and Gefter, W. I.: Use of Pronestyl in the Treatment of Ectopic Rhythms, Am. J. Med. **11**: 431 (Oct.) 1951.

2. (*a*) Berry, Garlett, Bellet, and Gefter.[1b] (*b*) McCord, M. C., and Taguchi, J. T.: A Study of the Effect of Procaine Amide Hydrochloride in Supraventricular Arrhythmias, Circulation **4**: 387 (Sept.) 1951.

3. Miyoko, I.; Millar, J., and Townsend, J. H.: Agranulocytosis Following Maintenance Dosage of Pronestyl: Report of Severe Case with Recovery, J. A. M. A. **147**: 652 (Oct. 13) 1951.

4. Mark, L. C., and others: The Action of Procaine Amide (N^1-[2-Diethylaminoethyl] p-Aminobenzamide) on Ventricular Arrythmias, abstract, J. Pharmacol. & Exper. Therap. **98**: 21 (Jan.) 1950. Kinsman, J. M.; Clay, H. L.; Coe, W. S., and Best, M. M.: Procaine Amide (Pronestyl) in the Treatment of Disorders of Cardiac Rhythm, Kentucky M. J. **48**: 509 (Nov.) 1950. Joseph, S. I., and Rovenstine, E. A.: Cardiac Arrhythmias: Prophylaxis and Therapy with Procaine Amide During Cyclopropane Anesthesia for Thoracic Surgery, abstract, J. Pharmacol. & Exper. Therap. **101**: 19 (Jan.) 1951. Joseph, S. I., and others: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrhythmias Occurring During Thoracic Surgery, Surg., Gynec. & Obst. **93**: 75 (July) 1951.

Knowledge of the pharmacology of procaine amide hydrochloride is far from complete, but one may theorize on possible causes for this fatal outcome. The hypotensive effect of intravenous procaine amide has been well described.[5] Death in this instance from such a cause seems highly improbable.

Another known effect is the widening of the QRS complex, and, in some instances, bundle branch block has developed. Recently McCord and Taguchi [2b] noted an increase in ventricular rate when procaine amide hydrochloride was administered to patients with auricular fibrillation. Such quinidine-like effects [6] might more easily cause ventricular fibrillation in a heart in which bundle branch block was already established. Caution in the use of quinidine in the presence of bundle branch block has been advised for years, but in practice this is honored more in the breach than the observance. It may be that such will be the case with procaine amide hydrochloride.

SUMMARY

A case of ventricular fibrillation with death immediately following an intravenous injection of procaine amide is reported. It is emphasized that caution is necessary in the use of this drug; increased caution is suggested in cases of bundle branch block.

P. O. Box 269.

5. Miyoko, Millar, and Townsend.[3] Procaine Amide Hydrochloride, Council on Pharmacy and Chemistry: New and Nonofficial Remedies, J. A. M. A. **144**: 1465 (Dec. 23) 1950. Stearns, N. S., and Callahan, E. J.: A Clinical Study of Intravenous Procaine Amide (Pronestyl): Its Value and Hazards, abstract, J. Clin. Investigation **30**: 676 (June) 1951. Edmonds, B. W.; Comer, W. H.; Kennedy, J. D., and Taylor, I. B.: Intravenous Use of Procaine in General Anesthesia, J. A. M. A. **141**: 761 (Nov. 12) 1949.

6. Gold, H.: Quinidine in Disorders of the Heart, New York, Paul B. Hoeber, Inc., 1950.

VENTRICULAR ACCELERATION FOLLOWING PROCAINE AMIDE HYDROCHLORIDE THERAPY

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Harold Miller, M.D.
George C. Griffith, M.D.
and
Morris H. Nathanson†, M.D., Los Angeles

Procaine amide ("pronestyl") hydrochloride has been recently introduced for the treatment of cardiac arrhythmias; its use has been found effective especially in rhythms of ventricular origin.[1] The drug appears to be relatively innocuous, and, aside from occasional mild to moderate hypotensive reactions, no serious untoward effects have been observed. It is known that cardiac depressant and antifibrillatory drugs, although effective in the elimination of ectopic rhythms, may at times induce ectopic ventricular rhythms, including ventricular fibrillation. Such cardiac effects have been observed during the course of quinidine sulfate therapy.[2] They have been observed with greater frequency after the administration of the potent antifibrillatory drug alpha-fagarine and related compounds.[3] In 55 patients with various auricular and ventricular arrhythmias, continuous electrocardiograms were made during and after the intravenous administration of procaine amide hydrochloride.[1d] We found no indication of drug-induced ectopic ventricular activity in this group. However, in three patients with complete heart block the intravenous administration of relatively small doses of procaine amide hydrochloride was followed by the appearance of frequent multifocal ectopic ventricular beats in two cases and a transient ventricular fibrillation in one.[4] It has been suggested that ectopic ventricular activity and ventricular fibrillation induced by quinidine sulfate therapy depends on an impaired function of the conducting system. The following report concerns a patient in whom pronounced widening of the QRS wave and a paroxysm of ventricular acceleration developed during and after the intravenous administration of procaine amide hydrochloride.

REPORT OF A CASE

The patient was a 69-year-old white woman, admitted to the hospital on Nov. 6, 1951. Her complaints were weakness, shortness of breath, and palpitation. She had had a myocardial infarction two years previously and had made an uneventful recovery. Since that time she had had dyspnea on mild effort. On the evening of admission, while walking to the grocery store, she experienced a sudden onset of palpitation, associated with weakness and shortness of breath, and was taken to the hospital.

On admission, she showed the following significant physical changes. She was moderately dyspneic, and there was a slight degree of cyanosis of the lips and finger tips. There was a pronounced distention of both jugular veins. Moist rales were present at both lung bases posteriorly. On auscultation, the heart rate was very rapid but appeared to be regular. The sounds were distant, and there were no murmurs. The blood pressure was 90 systolic and 70 diastolic. The abdomen was obese, but there were no palpable organs or masses. There was no edema of the extremities. The diagnosis was ectopic tachycardia and acute coronary occlusion as a possible basis for the arrhythmia.

An electrocardiogram was made shortly after admission, which showed a ventricular tachycardia, rate 210 per minute (*A* in the accompanying figure). The QRS wave was 0.1 second in duration, and there was a slurring of the R wave on the descending limb. Procaine amide hydrochloride, 500 mg., was injected by vein slowly at the approximate rate of 100 mg. per minute. This was followed by a gradual widening of the QRS; at one minute after the onset of injection, the QRS was 0.14 second and a notching appeared on the descending limb of the R wave (*D* in the accompanying figure). As the injection of the drug was

† Dr. Nathanson died on April 24, 1952.

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1. (*a*) Mark, L. C., and others: The Physiological Disposition and Cardiac Effects of Procaine Amide, J. Pharmacol. & Exper. Therap. **102**: 5 (May) 1951. (*b*) Kayden, H. J.; Steele, J. M.; Mark, L. C., and Brodie, B. B.: The Use of Procaine Amide in Cardiac Arrhythmias, Circulation **4**: 13 (July) 1951. (*c*) Kinsman, J. M.; Clay, H. L.; Coe, W. S., and Best, M. M.: Procaine Amide (Pronestyl) in the Treatment of Disorders of Cardiac Rhythm, Kentucky M. J. **48**: 509 (Nov.) 1950. (*d*) Miller, H.; Nathanson, M. H., and Griffith, G. C.: The Action of Procaine Amide in Cardiac Arrhythmias, J. A. M. A. **146**: 1004 (July 14) 1951. (*e*) Schaffer, A. I.; Blumenfeld, S.; Pitman, E. R., and Dix, J. H.: Procaine Amide: Its Effect on Auricular Arrhythmias, Am. Heart J. **42**: 115 (July) 1951. (*f*) Joseph, S. I., and others: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrythmias Occurring During Thoracic Surgery, Surg., Gynec. & Obst. **93**: 75 (July) 1951. (*g*) Morris, L. E., and Haid, B.: Effects of Procaine Amide on Cardiac Irregularities During Cyclopropane Anesthesia, Anesthesiology **12**: 328 (May) 1951.

2. (*a*) Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, Am. Heart J. **9**: 792 (Aug.) 1934. (*b*) Gold, H.: Quinidine in Disorders of the Heart, New York, Paul B. Hoeber, Inc., 1950. (*c*) DiPalma, J. R., and Schults, J. E.: Antifibrillatory Drugs, Medicine **29**: 123 (May) 1950. (*d*) Sokolow, M.: The Present Status of Therapy of Cardiac Arrhythmias with Quinidine, Am. Heart J. **42**: 771 (Nov.) 1951.

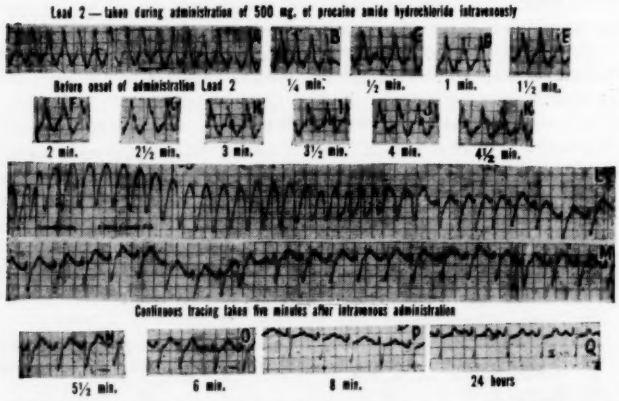
3. DiPalma and Schults.[2c] Scherf, D.; Silver, A. M., and Weinberg, L. D.: Clinical Observations with Fagarine, Ann. Int. Med. **30**: 100 (Jan.) 1949. Nathanson, M. H., and Miller, H.: The Effects of New Drugs on the Rhythmic Function of the Heart, California Med. **72**: 215 (April) 1950.

4. Miller, H., and Nathanson, M. H.: The Action of Procaine Amide in Complete Heart Block, to be published.

continued, there was a gradual reduction in heart rate and a widening and increased notching of the QRS (*E* through *K* in the figure. Strip *K* taken four and a half minutes after the start of the injection, shows the rate reduced from 210 to 160 per minute and the QRS wave widened to 0.2 second with pronounced notching on the descending limb. Five minutes after the start of the injection of the drug, a series of rapid regular ventricular oscillations appeared (*L* in the figure). There was a gradual reduction in the amplitude of these oscillations. This type of complex may be considered to represent a ventricular tachycardia from a new focus or a ventricular flutter. Such oscillations have been observed preceding the irregular oscillations of smaller amplitude, which are characteristic of ventricular fibrillation.[5] This was followed by ventricular complexes of approximately normal configuration, rate 140, a nodal rhythm (*M* in the figure). Auricular waves preceding the QRS gradually appeared, and restoration of sinus rhythm occurred eight minutes after the start of the injection (*P* in the figure). The patient was given 500 mg. of procaine amide hydrochloride every four hours. She had no further attacks, and subsequent observation showed no evidence of myocardial infarction.

COMMENT

Widening of the QRS wave has been observed during quinidine sulfate therapy and is considered as an indication for discontinuance of the use of the drug. Gold [2b] described a case of fatal syncope during the administration of quinidine sulfate, presumably due to cardiac standstill or ventricular fibrillation. An electrocardiogram taken after 5 gm. of the drug had been administered showed that the QRS, which had been normal before treatment, was prolonged to 0.16 second. In discussing the treatment of ventricular tachycardia, Gold stated



Electrocardiographic changes during the intravenous administration of 500 mg. of procaine amide hydrochloride to a patient with ventricular tachycardia.

that it is not wise to continue quinidine sulfate therapy if the QRS has been prolonged to 50% above the control. He expressed the belief that a widening of the QRS may represent a precursor to ventricular fibrillation. Sokolow,[2d] in a recent review, stated that he did not continue quinidine sulfate therapy after the increase in QRS time exceeded 50% of the control value and he used particular caution when the increase exceeded 25%. Kayden and co-workers [1b] noted that continuous intravenous infusion of procaine amide hydrochloride until death in the experimental animal produced the following events: prolongation of the P-R interval, widening of QRS complexes, wandering pacemaker, nodal and ventricular premature contractions, and ventricular tachycardia and fibrillation.

Davis and Sprague [6] and Davis [7] have emphasized the significance of the integrity of the conducting tissue in the prevention of ectopic ventricular rhythms. An intact conducting system distributes impulses quickly and uniformly to all regions of the ventricular myocardium. This not only insures harmony of contraction but further produces a uniform state of refractoriness. Such a generalized state of refractoriness protects against reentrant excitation. When there is impairment of ventricular conduction, the stimulus is delayed to portions of the heart and subsequently there is a variable state of refractoriness in the ventricular myocardium. The stimulus may then be blocked at hypoexcitable areas, continue along responsive paths, and reenter the blocked portion when it becomes responsive. This re-entry mechanism is considered to be the basis for ventricular rhythms, including ventricular fibrillation. For this reason it has been emphasized that, during the administration of such drugs as quinidine sulfate and digitalis, conduction defects are a warning sign of the onset of serious ventricular rhythms. In the present instance, the ventricular arrhythmia that occurred during the treatment was of short duration and had no untoward effects. However, it represents a prefibrillation state such as is frequently seen before the onset of fatal ventricular fibrillation. It would appear that, as with quinidine sulfate, widening of the QRS during procaine amide hydrochloride therapy is an indication for discontinuance of the use of the drug.

CONCLUSION

A case of ventricular tachycardia treated with procaine amide ("pronestyl") hydrochloride is reported in which the following events occurred: (*a*) progressive and pronounced widening and notching of the QRS wave of the electrocardiogram, (*b*) a short paroxysm of ventricular acceleration of a prefibrillation type, and (*c*) restoration of sinus rhythm. It is suggested that, as with quinidine sulfate therapy, a widening of the QRS wave during the administration of procaine amide hydrochloride may represent a precursor to ventricular fibrillation and is an indication for discontinuance of the use of the drug.

1200 N. State St. (Dr. Miller).

5. Schwartz, S. P., and Jezer, O.: Studies on Transient Ventricular Fibrillation: Observations on Alterations in Rhythm of Heart Preceding Syncopal Seizures in Patient with Normal Sinus Rhythm, Am. J. M. Sc. **187**: 469 (April) 1934. Schwartz, S. P., and Hauswirth, L.: Studies on Transient Ventricular Fibrillation: Observations on Alterations in Rhythm of Heart Preceding Syncopal Seizures in Woman with Transient Auriculoventricular Dissociation, ibid. **187**: 478 (April) 1934.

6. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block: Report of Case in Which Syncopal Attacks and Death Occurred in Course of Quinidine Therapy, Am. Heart J. **4**: 559 (June) 1929.

7. Davis, D.: Ventricular Tachycardia: An Interpretation of the Nature of its Mechanism, Am. Heart J. **7**: 725 (Aug.) 1932.

Basal Metabolic Rate.—Either hypothyroidism or hyperthyroidism may be present in the face of a basal metabolic rate that falls within the normal range. Moreover, a low basal metabolic rate does not always indicate hypothyroidism, but may represent hypometabolism without hypothyroidism. Contrariwise, an elevated basal metabolic rate does not invariably mean hyperthyroidism. In the absence of thyrotoxicosis high values may be encountered in such diverse states as Paget's disease, polycythemia, anemia, leukemia, lymphosarcoma, Hodgkin's disease, essential hypertension, aortic stenosis, coarctation of the aorta, and dyspnea due to cardiac or pulmonary disease. Elevations of the basal metabolic rate may also result when the patient is inadequately rested or fasted, overexcited, or has a tremor or a punctured tympanic membrane.—J. L. Gabrilove, M.D., and W. R. Dorrance, M.D., Tests of Endocrine Function. *The Medical Clinics of North America*, May, 1952.

FEVER DUE TO PROCAINE AMIDE HYDROCHLORIDE THERAPY

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and
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Procaine amide ("pronestyl") hydrochloride is a drug widely used for the elimination and prevention of ectopic ventricular rhythms. Its oral use at times is maintained for long periods to prevent recurrent premature beats or paroxysmal ventricular tachycardia. Toxic side-effects have been infrequent and usually not serious. Minor toxic affects have been gastrointestinal irritation with anorexia, nausea, and vomiting, usually occurring with a high dosage (6.0 to 8.0 gm. a day).[1]

A major toxic effect has been the production of granulocytopenia following bone marrow depression with death.[2] We recently observed a patient in whom chills, fever, generalized muscle pains, malaise, dermatitis, and mental depression developed during the administration of the drug. The fever disappeared abruptly when use of the drug was discontinued and recurred on two subsequent occasions after readministration of the drug. The causative relation of the drug to the fever seemed definite. We had not previously encountered a similar instance, but, during the preparation of this report, we found an article by Leibowitz [3] describing a patient in whom chills and fever developed after oral ingestion of procaine amide hydrochloride. He predicted, "As experience with procaine amide increases it is likely that similar reactions will be encountered." In our patient, much laboratory work was done in an attempt to explain the cryptogenic fever before the drug was suspected as causative. It is probable that other instances are occurring and are unrecognized, especially if the patient is ambulatory and not under close observation. Chills, fever, muscle aches, and malaise could easily be ascribed to current viral infections or other plausible causes. Procaine amide hydrochloride must be suspected as a possible cause of any febrile reaction occurring during its administration.

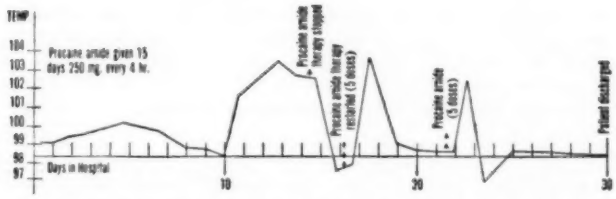
REPORT OF A CASE

A 58-year-old unmarried woman was first seen in the office Jan. 22, 1952, complaining of bilateral anterior chest and shoulder pain, with extension to both arms and to the interscapular region, of six days' duration. An electrocardiogram demonstrated unequivocal evidence of acute posterior myocardial infarction. The patient was immediately hospitalized. Anticoagulant treatment was started, with intravenous administration of heparin and oral administration of bishydroxycoumarin (dicumarol®). Procaine amide hydrochloride, 250 mg. every four hours day and night, was given on admission because of the presence of frequent premature ventricular beats. The patient's temperature on admission was 98.2 F.

During the following 10 days the oral temperature fluctuated diurnally, reaching a high of 100.4 F (see the accompanying figure). This low grade febrile response was accepted as commensurate with cardiac infarction.

On the 11th hospital day, the oral temperature rose to 101.8 F. The patient became nauseated and vomited. She was irritable and apprehensive. During the succeeding four days the temperature remained elevated, reaching a maximum of 104 F. The white blood cell count was 5,000. The cause of the sudden rise in temperature and the clinical picture of malaise, nausea, and vomiting was not clear. Septicemia, genitourinary infection, pulmonary infarction, brucellosis, typhoid, and peripheral thrombophlebitis were considered and investigated with appropriate laboratory studies. After five days of continuous fever, although no one was familiar then with reports of fever due to the use of bishydroxycoumarin or procaine amide hydrochloride, it was thought that the reaction might be caused by one of these.

On the 15th day at 6 a. m., the administration of both bishydroxycoumarin and procaine amide was discontinued. The temperature began to drop and 24 hours later was normal; it remained so during the following 36 hours. Improvement in the patient was immediate and dramatic. The aching and malaise disappeared; the mental irritability and apprehension was succeeded by cheerfulness. The nurses' record said, "She has no complaints." Two days later the procaine amide therapy was started again, 250 mg. every four hours for five doses. The first dose was given at 10 a. m. By 4 o'clock in the afternoon the patient felt distinctly uncomfortable and mentally irritable and by 11 o'clock the temperature was 104 F. The next morning she was nauseated, mentally irritable, and depressed, talking incessantly and wanting to go home. The following day the temperature was normal; she felt much better, appeared normal, and listened with interest to the radio. For five days she felt well and the temperature was normal.



Fever following oral administration of procaine amide hydrochloride. The fever subsided with discontinuance of the use of the drug and recurred when it was readministered on two occasions.

After five days procaine amide therapy was started again. After the third dose the patient recognized the effect of the drug and said, "It is those little yellow pills that are upsetting me." The temperature again rose to 104 F; the next day a maculopapular, itching rash appeared on the extensor surfaces of the arms, feet, thighs, and dorsa of both feet. Again, after discontinuance of the use of the drug, the temperature became normal the next day, and the rash faded. During the remainder of her hospital stay she had no further trouble.

SUMMARY

An instance of fever, chills, rash, and malaise following oral administration of procaine amide ("pronestyl") hydrochloride is reported.

1930 Wilshire Blvd. (5) (Dr. Askey).

From the Department of Medicine of the University of Southern California School of Medicine and the Medical Division of St. Vincent's Hospital.

1. Kayden, H. J.; Brodie, B. B., and Steele, J. M.: Use of Procaine Amide in Cardiac Arrhythmias, Mod. Concepts Cardiovas. Dis. **20**: 100 (June) 1951.

2. Miller, H.; Pollock, R. C., and Griffith, G. C.: Fatal Agranulocytosis Resulting from a Procaine Derivative, J. Lab. & Clin. Med. **38**: 850 (Dec.) 1951.

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ALLERGY TO PROCAINE AMIDE

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The therapeutic similarity between procaine amide and quinidine is recognized; however, whereas the toxic effects of quinidine are well known, procaine amide ("pronestyl") has not yet been used widely enough to permit evaluation of its ability to cause toxic reactions. The following case of a true allergic reaction to procaine amide is, therefore, discussed.

REPORT OF A CASE

A 53-year-old man with known hypertension for the past 20 years was first seen on Nov. 11, 1951, with sudden onset of severe substernal oppression. An electrocardiogram revealed acute anteroseptal myocardial infarction. On Dec. 11, 1951, the heart rate, which had been 85 per minute, increased to 115, and numerous extrasystoles, subsequently shown by electrocardiograph to be auricular premature contractions, were noted. The patient was given 1.5 gm. of procaine amide orally; this was followed by 250 mg. every four hours. After the third dose, when a total of 1 gm. had been taken, a generalized maculopapular erythematous rash developed, accompanied by severe itching, congestion of the nose, slight generalized adenopathy, and a fever of 102 F. Cessation of procaine amide therapy and institution of diphenhydramine (benedryl®) hydrochloride, 50 mg. every 4 hours, was followed by complete subsidence of all symptoms within 24 hours.

Inasmuch as the patient was receiving other medication at the time of this reaction, it was decided to test him with procaine amide alone. Consequently, on Feb. 10, 1952, he was placed on 250 mg. of procaine amide every four hours. Following the fourth dose, the identical clinical picture noted above developed; this condition again promptly responded to diphenhydramine hydrochloride. A stained blood smear at the height of the reaction showed 7% eosinophils as compared with ½ to 1% in the control smear before beginning the procaine amide test. A subsequent patch test with the drug was negative.

COMMENT

Hitherto, reported toxic effects of procaine amide had been limited to the circulatory and gastrointestinal systems.[1] Recently, reference has been made to three cases of agranulocytosis [2] and two cases of urticaria [3] following its use. Although it is not unusual to find a patient who is sensitive to quinidine and who has fever and a skin eruption following even small doses, such a reaction to procaine amide has not been previously reported.

923 Fifth Ave.

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HUMAN POISONING BY CHLORDANE

REPORT OF A CASE

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The newer insecticides have proved their value in control of insects.[1] Since the products have been made available to the public, however, accidental poisonings have occurred. We are reporting our experience in such a circumstance.

Chlordane, a chlorinated hydrocarbon having the empirical formula $C_{10}H_6Cl_8$, is in the pure state a viscous, amber-colored, odorless liquid. It can be formulated for use in varying strengths as an oil solution, an emulsion concentrate, a dust, or a wettable powder.[2] Human toxicity of these preparations depends on the type of vehicle as well as the concentration of chlordane. Some of the toxic manifestations ascribed to chlordane preparations may be due to the vehicle alone.[3] Contamination of the skin with certain petroleum distillates has produced anesthesias and paresthesias that may be due to the fat solvent properties of the distillates.[4]

The insecticide enters the body by absorption through the intact skin, by inhalation of dusts or sprays, and by ingestion. Skin and intestinal absorption is enhanced by the presence of fats, oils, or organic solvents.[5] Chlordane is moderately irritating to the skin in concentrated form, but in the diluted solutions commonly used this skin warning fails to appear. As little as 2.4 gm. in solution contacting the skin daily may be dangerous to man.[6] Acute fatal poisoning may result from a dose of 5 to 60 gm.[7] The onset of symptoms may occur as early as 45 minutes following ingestion of chlordane. Death may result within 24 hours, but most commonly not until the third or fourth day. If survival continues to the sixth day, recovery usually follows. Irritability of the central nervous system is the earliest sign and symptom. This irritability progresses into convulsions alternating with periods of depression.[8] Death occurs following deep central nervous system depression with or without a terminal seizure.[7] Chronic poisoning produces predominately inanition, probably due to the severe degenerative changes in the liver, the most severely damaged of the vital organs. These changes are similar to those produced by other chlorinated hydrocarbons such as chloroform.[8] Degenerative changes in the proximal convoluted tubules of the kidney [9] and subserosal hemorrhages in the intestines and heart have been demonstrated in animals.[10]

Prophylaxis should be directed toward preventing acute and chronic exposures to the poison through the skin and respiratory tract in the manufacture, in formulation of commercial compounds, and in the ultimate use by the public. This and a decrease in the accidental ingestion may be brought about by stressing the human toxicity of this substance. Actual treatment involves removal of the poison from the gastroenteric tract and skin as rapidly as possible by any means available. Convulsions should be controlled by sedatives or general anesthesia. Stimulants, and other supportive measures such as oxygen, should be used in the phases of central nervous system depression.

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REPORT OF A CASE

C. J. E., 15-month-old daughter of one of the authors, accidentally drank a small amount, probably not more than a mouthful, of a chlordane suspension. This occurred at about 3 p. m. Although the child spit out some of the suspension, the mother promptly induced vomiting by administering sodium bicarbonate solution and gagging the child. This was accomplished within 2 to 3 minutes following ingestion. The chlordane suspension was made using 1 tablespoon of a wettable powder (50% chlordane) suspended in 1 qt. (1 liter) of water. The distributor of the commercial preparation, the county agricultural agent, and a biochemist were consulted. All were of the opinion that the amount taken was probably not toxic, although all admitted there was not sufficient information available to them concerning chlordane's toxicity.

About three hours after ingestion (6 p. m.) a generalized tremor developed, and the child became incoordinate and ataxic, falling several times. Convulsions soon ensued, tonic phases alternating with short clonic phases, until they were controlled by ethyl chloride inhalations about 40 minutes later. On examination when the convulsions began her temperature was 99.6 F rectally, the pupils were dilated but reacted to light, her face was flushed, the respirations were irregular, and the pulse rate was 140 per minute. Risus sardonicus, opisthotonos, bilateral ankle clonus, and generalized hyperactive reflexes were present. Cyanosis was noted only during administration of ethyl chloride. After the convulsions were controlled by ethyl chloride inhalations, amobarbital (amytal®) sodium was given (0.06 gm. intravenously and 0.06 gm. subcutaneously) to facilitate gastric lavage with magnesium sulfate saturated solution. The strong odor of chlordane suspension was apparent in all washings. Some of the magnesium sulfate was left in the stomach. At 7:30 p. m. (4½ hours after ingestion of chlordane) the convulsions seemed controlled, and the patient was admitted to a hospital. Thirty minutes later generalized convulsions recurred and were not controlled until 0.345 gm. of amobarbital sodium was administered intravenously, and 0.06 gm. subcutaneously. Oxygen and fluids intraveneously were given continuously. For the next eight hours respirations were irregular in rate and shallow in depth except for an occasional deep sigh. We were unable to determine whether the respiratory depression was due to the chlordane ingested or to the large amount of amobarbital sodium given. Thirteen hours after chlordane ingestion respirations resumed normal character, and 16 hours after chlordane ingestion the child roused. Examination at this time revealed irritability, dilated pupils, and some ataxia. For the next few hours the child was constantly moving, unaware of her surroundings, and irritable when disturbed. The pupils resumed normal size, and respirations continued to be regular.

During the second day the consulting neurologist found only moderate ataxia and irritability. This irritability prevented the obtaining of an electroencephalogram; however, an electrocardiogram and chest roentgenogram were made, and the patient was discharged from the hospital. The ataxia and irritability progressively diminished and finally disappeared after two to three weeks.

Past History.—The child had had no convulsions previously. She had always been in good health, and her development had been normal.

Laboratory Data.—On the day following admission a blood count revealed only mild hypochromic anemia. On this day and the following day her urine contained an occasional white blood cell and red blood cell in a centrifuged specimen. The electrocardiogram was within normal limits, and chest roentgenogram revealed no abnormality of the heart or lungs. An attempt was made to obtain an electroencephalogram three weeks later but was unsuccessful, owing to lack of cooperation by the patient.

COMMENT

Individual susceptibility to chlordane varies within wide limits, probably even more than is at present determined. In our case the quantity ingested unfortunately could not be determined exactly, but it is our impression that the amount of chlordane ingested by this child weighing 9 kg. did not exceed 100 mg. Because of the individual susceptibility, treatment should be immediate and directed toward the prompt removal of chlordane from the body, no matter how small the amount. Careful gastric lavage in our case was not done immediately because the information we obtained indicated that the amount ingested was too small to be of concern. As Lehman has well stated, "Absolute toxicity of any given insecticide is of relatively minor interest, but the real criterion of utility must ultimately be based on the hazards to man. . . . Little effort is directed towards the study of long-range effects on plant and animal life before the insecticide is introduced into commerce."[11]

SUMMARY

A case of poisoning due to a new popular commercial insecticide, chlordane, demonstrates the signs and symptoms of toxicity. The need for adequate investigation and dissemination of information concerning the dangers of insecticides to man is stressed.

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MENINGITIS DUE TO PSEUDOMONAS AERUGINOSA

INTRATHECAL TREATMENT WITH STREPTOKINASE AND STREPTODORNASE AND INTRAMUSCULAR AND INTRATHECAL TREATMENT WITH NEOMYCIN

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and
Juan Negrin Jr., M.D., New York

The over-all mortality from meningeal infection with Pseudomonas aeruginosa was found by Stanley to be 68% in a review of 90 cases reported to 1947.[1] The same author observed that, when the cases were divided into groups depending on whether the infection was primary in the meninges or whether it had developed secondary to foci elsewhere in the body, there was a pronounced difference in the case fatality rate. Patients in whom meningitis was the primary disease, comprised mostly of persons who were infected by lumbar punctures or after neurosurgical procedures, showed a mortality rate of 55%. Patients in whom the meningitis occurred as a complication of infection originating elsewhere in the body showed a mortality rate of 86%. From these data it is apparent that meningitis due to Ps. aeruginosa is a serious disease. Moreover, it is our opinion that published

This study was supported in part by a grant from Charles Pfizer & Company, Brooklyn.

From the Department of Medicine and Neurosurgery, Cornell University Medical College and the Cornell Medical and Surgical Divisions, Bellevue Hospital.

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reports tend to minimize the mortality figures, since it seems certain that more recoveries than fatalities are deemed worthy of reporting.

Antimicrobial treatment of Ps. aeruginosa meningitis has only occasionally been successful, with the most favorable results obtained by the use of polymyxin B. Tomlin,[2] Hayes,[3] and Jawetz,[4] and their respective associates, have reported the successful treatment of one patient each with this agent. Two of the patients experienced severe local pain at the time the intrathecal injections were administered, and the two who received the material intramuscularly exhibited transient signs of nephrotoxicity, consisting of casts in the urine and albuminuria. Two patients relapsed after initial control of the disease but were later successfully re-treated.

Although this appears to be the most effective antimicrobial agent available for treatment of meningitis due to Ps. aeruginosa, one must maintain some reservations concerning the use of an agent in which the toxic concentration is so close to the therapeutic concentration.

Another approach to the treatment of meningitis that has recently received some clinical appraisal is the intrathecal administration of streptococcic concentrates containing streptokinase and streptodornase. This treatment has proved highly beneficial in cases of empyema and infected hemothorax, and on occasion sterilization of chest cavities has resulted without concomitant antimicrobial therapy.[5] It has been demonstrated that the streptococcic concentrate may cause lysis of purulent and sanguineous exudate,[6] with the result that infecting bacteria may be more directly exposed to host defenses or antimicrobial therapy. Presumably this is the basis for the activity of these substances in meningitis.

Recently we had an opportunity to treat a patient with meningitis due to Ps. aeruginosa that had developed after an elective laminectomy. The treatment employed consisted of intrathecal injections of a solution of streptokinase and streptodornase and intrathecal and intramuscular injection of neomycin. The results were highly favorable, and details of the patient's course constitute the present report.

REPORT OF A CASE

The patient, a 26-year-old white housewife, was first admitted to Bellevue Hospital on Jan. 29, 1951, with a history and physical findings consistent with the presence of a herniated intervertebral lumbar disk. The defect could not be demonstrated by myelogram. On March 14 a right hemilaminectomy of the fifth lumbar vertebra was performed, and a small disk impinging on the nerve root was found. The protruded disk was excised, leaving the dura intact. Twenty-four hours after operation, the patient's temperature rose to 105 F and slight nuchal rigidity was noted. Examination of the wound revealed evidence of infection at its upper end. Separation of the skin margins permitted drainage of approximately 12 cc. of seropurulent material. The infection appeared to arise from the depths of the wound, which was explored down to the dura. No foreign body was found. Cultures of the wound revealed a diphtheroid bacillus, and for this reason penicillin was given intramuscularly in large doses. After five days the patient's temperature returned to normal. On the seventh postoperative day nuchal pain and rigidity were again noticed, and wound cultures at this time revealed Ps. aeruginosa. Despite the presence of this organism, healthy granulations gradually filled the wound, signs and symptoms subsided, and the patient was discharged with the wound virtually healed on May 3. Lumbar puncture was not done postoperatively.

Five days later, on May 8, the patient was readmitted to the hospital, complaining of headache, stiff neck, vomiting, chills, and fever. The operative wound appeared well healed, and there was no local tenderness. Lumbar puncture revealed cloudy xanthochromic fluid, which contained 1,420 white blood cells per cubic millimeter; cultures revealed Ps. aeruginosa. During the next six weeks, the patient received continuous antibiotic therapy in high dosage; penicillin, chloramphenicol, terramycin, and streptomycin were given in various combinations. In the course of the treatment she received three intrathecal injections of streptomycin, 0.05 gm., at two-day intervals. Despite this treatment, she continued to have daily temperature elevations to 101 or 102 F. Cerebrospinal fluid sugar concentrations were low, ranging from 15 to 34 mg. per 100 cc. The chloride level ranged from 80 to 141 mg. per 100 cc., and several protein determinations were approximately 75 mg. per 100 cc. About 1,500 white blood cells per cubic millimeter were consistently observed in the cerebrospinal fluid, and approximately 2,500 red blood cells were noted on several occasions. Several cultures of the cerebrospinal fluid revealed Ps. aeruginosa, and on one occasion this organism appeared in a culture of the blood.

In view of the unremitting infection we decided to explore the wound again. Accordingly, on June 3 a total laminectomy of the fifth lumbar vertebra was done, with exploration of the epidural space. Abscess, foreign body, or other abnormality was not found.

Drug susceptibility tests revealed the organism to be resistant to 25 μg per cubic centimeter of chloramphenicol, aureomycin, and streptomycin. It was found to be sensitive to neomycin (4 units per milliliter in 24 hours). As the patient's condition continued to deteriorate despite three months of intensive antimicrobial therapy, we decided to institute intrathecal treatment with streptococcic concentrate (streptokinase and streptodornase) and neomycin.[7] The patient was given 15,000 units of streptokinase and 3,750 units of streptodornase intrathecally at two-day intervals, with daily intrathecal administration of 5,000 units of neomycin. Neomycin was also given intramuscularly in a daily dose of 120,000 units. The patient continued to receive penicillin. Details of this portion of her course may be seen in the accompanying chart. Her temperature rose to 105.8 F 12 hours after the first intrathecal administration of streptokinase and streptodornase, despite the fact that treatment with corticotropin (ACTH), 75 mg. daily, had been started 24 hours previously. During intrathecal administration of the enzyme solution, and for about one hour thereafter, the patient complained of discomfort of the lower part of the back and saddle area and experienced a dull headache of moderate severity. Lumbar puncture six hours later, however, failed to reveal any significant changes over pretreatment findings. She felt nauseated for several hours. Twenty-four hours after the initial intrathecal medication the patient became semistuporous and disoriented, and there was pronounced increase in nuchal rigidity. The cerebrospinal fluid pressure at this time was 330 mm. of water, and the fluid appeared distinctly more turbid. Great relief followed the slow withdrawal of 25 cc. of cerebrospinal fluid. On the alternate days, in which neomycin was administered intrathecally without enzymes, no subjective discomfort was noted, and there was no temperature elevation or other objective evidence of untoward effect. Cerebrospinal fluid cultures were continuously sterile after the second day of treatment. Chills and temperature elevations to 103 to 105 F occurred 8 to 12 hours after the patient received the remaining two intrathecal injections of streptokinase and streptodornase, and cerebrospinal fluid pressure following the third administration was 520 mm. of water. Sufficient amounts of cerebrospinal fluid were withdrawn to lower the

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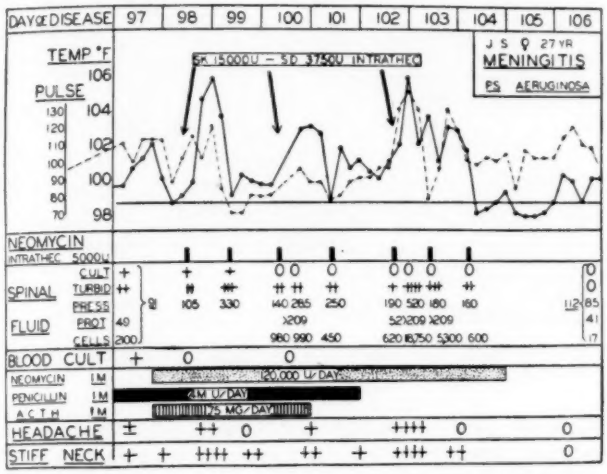
pressure either to normal or to half the initial pressure. Papilledema did not develop. Blood pressure remained fairly constant, while the pulse rate varied proportionately with temperature fluctuations. Urine output was good and remained free of albumin, casts, and blood cells. The plasma nonprotein nitrogen concentration was determined before, during, and after treatment and did not exceed normal limits. Cerebrospinal fluid turbidity rapidly diminished after the completion of treatment, and by the ninth day it was crystal clear. The patient gradually improved; by the time of her discharge, one month after the cessation of treatment, she was without significant abnormal physical signs and had no symptoms. At the time of writing, she had been followed for a period of nine months and had remained well.



Course of patient with meningitis due to Ps. aeruginosa during intrathecal treatment with streptokinase and streptodornase. Neomycin was concomitantly administered both intramuscularly and intrathecally. A severe toxic reaction followed each intrathecal injection of streptokinase and streptodornase, but sterilization of cerebrospinal fluid occurred promptly, followed by complete recovery.

COMMENT

It is difficult to assess the role of the agents used in the successful treatment of the patient. In vitro tests indicated that neomycin was highly active against the strain of Ps. aeruginosa in the cerebrospinal fluid, and its use may have contributed materially to the control of the infection. The effect of treatment with streptokinase and streptodornase is more difficult to evaluate. There are no satisfactory clinical signs or tests by which one can reliably measure the therapeutic effect of these substances in the subarachnoid space. Moreover, the presence or absence of febrile reactions and other evidences of toxicity do not appear to correlate with the therapeutic effect and, in fact, may represent in part chemical irritation by other substances in the streptococcic concentrate. In the evaluation of the treatment of this patient, two further points are worthy of comment. First, the fact that recovery has been reported in three cases in which polymyxin B alone was used (despite two relapses) indicates that antimicrobial therapy alone may be effective. Second, Tillett and his co-workers have reported the recovery of a patient with meningitis due to Ps. aeruginosa following one intrathecal injection of streptokinase.[8] The recovery occurred after several months of failure to cure the patient with intensive antimicrobial therapy (although neomycin or polymyxin B were not given). In this case there was little doubt that the use of streptokinase and streptodornase was responsible for the patient's recovery, whether by permitting exposure of the infecting organism to the previously ineffective antimicrobial agents or by assisting host defenses by lysis of the exudate. The further possibility that the streptococcic concentrates might directly affect Pseudomonas organisms cannot be entirely excluded, but in vitro tests have failed to show inhibitory activity by this substance. Moreover, there was no change of the inhibitory activity of chloramphenicol against a strain of Ps. aeruginosa when streptococcic concentrate was added to the test.[9]

From the case reported by Tillett and his associates, and the one presently under discussion, it appears that intrathecal injection of streptokinase and streptodornase may be of therapeutic value in the treatment of meningitis caused by Ps. aeruginosa.

The toxic reactions in the present case appeared to result from the enzyme therapy, since they occurred after each intrathecal injection and did not occur when neomycin was given alone. In fact, neomycin was well tolerated without apparent evidence of local or systemic toxicity. The chills, high fever, increased cerebrospinal fluid pressure, and lethargy appeared to be referable to a local action of the injected enzyme, and striking relief was obtained by the slow withdrawal of a few cubic centimeters of spinal fluid. The reactions could be explained on the basis of a rapid accumulation of cerebrospinal fluid and increased intracranial pressure after administration of the enzymes.

As has been mentioned previously, the severity of the toxic responses does not appear to be in proportion to the therapeutic effect, and conceivably the reactions could be minimized with further studies of dosage and method of administration of the agent. The toxicity may be serious, however, and in two patients with tuberculous meningitis death occurred a few hours after intrathecal injection of enzyme.[10] At present, a number of other patients with purulent meningitis have received intrathecal enzyme therapy and have tolerated the injections with a minimum of difficulty. The corticotropin was administered in an attempt to minimize the anticipated reaction to therapy, but it apparently had little effect. It does not seem possible to attribute an important role to corticotropin in the treatment of this patient.

The choice of neomycin in the present case was based on knowledge of its in vitro activity against the offending organism. So far as is known there would be no objection to combining treatment with polymyxin B or other antibiotics with intrathecal enzyme therapy. Such a combination might permit shorter periods of treatment with potentially toxic agents and, at the same time, forestall the occurrence of relapses, such as occurred in two of the three patients receiving polymyxin B alone.

SUMMARY

A patient with meningitis due to Pseudomonas aeruginosa, resistant to treatment with several antimicrobial agents, completely recovered after a course of intrathecal treatment with streptokinase and streptodornase and intrathecal and intramuscular treatment with neomycin.

First Ave. & 26th St.

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9. Unpublished observations of this laboratory.

10. Craddock, W. L., and Haddock-Suarez, J.: Terminal Hyperthermia Following Intrathecal Streptokinase Administration in a Case of Tuberculous Meningitis, Ann. Int. Med. 36: 168-171, 1952. Guthrie, T. C.: Unpublished data.

SIMPLE TRACTION DEVICE

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Recently, we were confronted with the problem of providing a method for mobilization of contractures in both hips and knees of a patient in whom none of the usual orthopedic or physical therapeutic techniques was applicable. The problem was successfully solved with the aid of a simple traction device that was built in a short time without the use of complicated machinery. The purpose of this paper is to make generally available the knowledge of this additional, easily constructed physical therapeutic aid.

The construction of this device is illustrated diagrammatically in figure 1. We used a masonite® board ⅜ in. by 16 in. by 18 in. and two pieces of plywood, each ½ in. by 6 in. by 6 in. The latter were made into two small carriages by attaching four small metal wheels to each. The wheels could spin freely because friction was low. The carriages moved easily with only slight pushing or pulling. Such pushing or pulling force was provided by the weight of the patient's legs while the device was in operation.

REPORT OF A CASE

A 40-year-old white salvage dealer sustained third degree burns while cutting up an old car with an acetylene torch. The gas tank had exploded, and burning gasoline had doused his legs. For nine weeks the patient was treated in various hospitals and at home. When he finally came to the hospital, he had lost 50 lb., and strong flexion contractures in both hips and knees had developed. Passive range of motion in these joints was about 10 degrees; active movements were almost completely lacking. Black leathery eschar covered part of the burned areas on both lower legs and feet. Greenish, purulent discharge came from beneath the fissures. Wet compresses were ordered to prepare the wounds

Fig. 2.—Position of patient's legs at beginning of traction therapy.

for skin grafting. In the meantime the patient was referred to the department of physical medicine for restoration of normal function of the contracted joints and for strengthening of the severely atrophied muscles of both legs.

None of the usual orthopedic or physical therapeutic techniques for mobilization of hip or knee contractures could be used in this case. Adhesive tape traction requires healthy skin, of which the patient did not have enough left; skeletal traction could not be considered, because it would have been necessary to drill the Kirschner wire through denuded and infected skin, which could result in osteomyelitis; passive and assistive motion would have been too painful, because the legs could not be gripped without including parts of the burned areas; manual traction could not be performed, because what healthy skin was left had become macerated from the wet packs and was too slippery to provide a firm grip. Nevertheless, the joints had to

Fig. 3.—Position of patient's legs, with contractures corrected, 24 hours after traction therapy was instituted.

be moved by some method as soon as possible to prevent a seriously crippling condition to result from the contractures.

The problem was solved by use of the traction device described. The masonite® board and the two small carriages were put on the bed. Both heels were gently lifted onto gauze "doughnuts" and, with these, onto the carriages (fig. 2). A folded towel was placed under the foot end of the masonite® board to produce an inclined plane, with the foot end of the board higher than the head end. This was necessary because the patient's pain was too severe while the board was in the horizontal position. With the board inclined in the only position the patient could tolerate, it was noted that the carriages had a tendency to roll toward the head, thus increasing the flexion contractures; however, the weight of the legs not only nullified this tendency but even made the carriages move gradually against gravity toward the foot end of the board. It was hoped this would eventually straighten out the contractures. The patient was left in this position, since he did not complain of pain. To the surprise of all concerned, the patient's legs were almost straight after only 24 hours on the traction device (fig. 3). The patient then started active hip and knee exercises, using the device for assistive force as long as his muscles were too weak to perform these movements unassisted. When skin grafting was done, on one leg at a time, exercises were continued on the leg not being surgically treated. Exercises were resumed on the leg that had been operated on as soon as the graft had sufficiently taken. The subsequent hospital course was uneventful.

SUMMARY AND CONCLUSION

Multiple joint contractures were straightened out quickly, yet gently, by the use of a simple traction device. This device also provided assistance to the atrophied muscles for active motion. The same equipment can be used effectively for arthritic patients or postoperatively in cases in which an effective traction device is required. The tractive force is easily regulated by merely changing the incline of the board according to the patient's tolerance. The apparatus is inexpensive and can be improvised without difficulty.

From the Veterans Administration Hospital, Jefferson Barracks, Mo.

Because of space limitations, figure 1 has been omitted from THE JOURNAL and will appear in the authors' reprints.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

CONGENITAL THYROID HYPERPLASIA IN TWINS

REPORT OF A CASE FOLLOWING ADMINISTRATION OF THIOURACIL AND IODINE TO MOTHER DURING PREGNANCY

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J. C. Foushee, M.D.
and
J. I. Palmer, M.D., Thomasville, Ga.

The purpose of this communication is to record the occurrence of hyperplasia of the thyroid in newborn twins following the administration of thiouracil and iodine to the mother during gestation. To our knowledge no other case of apparently induced hyperplasia of the thyroid in humans has been reported. Experimentally hyperplasia of the thyroid has been produced in puppies by thyroidectomy upon the mothers. In regions where endemic goiter prevails, the occurrence of spontaneous congenital enlargement of the thyroid is not rare.

REPORT OF CASE

History.—The first of normally delivered twin girls was stillborn. The mother, aged 36, who had previously borne six healthy children, was receiving treatment for thyrotoxicosis. For five months she had received strong iodine (Lugol's) solution, 10 drops three times daily, and propylthiouracil, 100 mg. four times daily, with amelioration of her symptoms and reduction of the basal metabolic rate from +36 to +11%.

External Examination.—The examination of the stillborn infant began one hour after delivery, Nov. 23, 1951. Permission to open the head was not obtained. Externally the cadaver appeared normal, except that there was a conspicuous smooth tumor, 3 cm. in diameter, at the middle of the neck. The body length (estimated) was 65 cm., the weight 3,000 gm. The entire skin surface was smooth and pink, with no lividity anywhere. There was no rigor mortis. The orifices were empty and without discoloration.

Internal Examination.—The single abnormal finding was the enlarged thyroid, which measured 4.5 by 3.5 by 2.5 cm. and weighed 32 gm. The cut surface was uniform, being slightly reddish, slightly firm, and homogeneous except for slender lobular septums. The lungs were totally unexpanded; the left myocardial wall was contracted. The thymus, the adrenal glands, and all other thoracic, abdominal, and pelvic viscera were normal.

Histological Study.—The sections of the thyroid were uniform and consisted of closely arranged empty follicles separated by loose reticular tissue in which there were numerous capillaries. The follicles varied only moderately in size and were lined by simple cuboidal epithelium, with no parathyroid tissue in any of the sections. There was no demonstrable lesion of the thymus, adrenals, kidneys, liver, pancreas, or spleen. The prenatal atelectasis of the lungs appeared uncomplicated.

The surviving twin sister has an enlarged thyroid but appears normal otherwise.

SUMMARY

The occurrence of congenital hyperplasia of the thyroid, apparently induced, in twins, one of them stillborn, is reported.

From the pathology, surgical, and obstetrical services, John D. Archbold Memorial Hospital.

COUNCIL ON PHARMACY AND CHEMISTRY

REPORT TO THE COUNCIL

The following abstract of recent nomenclature decisions of the Council is authorized for publication.

R. T. Stormont, M.D., *Secretary.*

NEW GENERIC AND BRAND NAMES RECOGNIZED BY THE COUNCIL

The Council collaborates with manufacturers in the selection of generic and brand names for marketed drug preparations presented for acceptance and also for new products still under development or clinical trial. The last report on such names appeared in The Journal, May 3, 1952, p. 63.

The following abstract lists the generic designation, the chemical name, where necessary for information, and the brand name or names simultaneously recognized for the stated firms. In general, a generic name should bear recognizable relation to the chemical name and conform as closely as consistent with brevity and practicality to existing systems of scientific nomenclature. The chief requirement for a brand name is that it should not be therapeutically suggestive.

The listing of a brand name is not to be construed as indicating Council acceptance of the product itself. Products accepted for inclusion in N. N. R. are announced separately.

Basic Aluminum Carbonate Gel for an aluminum hydroxide-carbonate complex: Baseljel (Wyeth, Inc.)

Bimethoxycaine Lactate for Bis[β-(*o*-methoxyphenyl)isopropyl]amine lactate: Isocaine Lactate (The Upjohn Company)

Calcium *p*-Aminosalicylate: Pasara Calcium (Smith-Dorsey)

Carbacrylamine Resins for the following combination of the component ion exchange resins: carbacrylic resin, potassium carbacrylic resin, and polyamine-methylene resin: Carbo-Resin (Eli Lilly and Company)

Carbacrylic Resin and Potassium Carbacrylic Resin for the hydrogen and potassium forms of cross-linked polyacrylic polycarboxylic ion exchange resin

Chlormerodrin for the mercurial diuretic compound 3-chloromercuri-2-methoxypropylurea: Neohydrin (Lakeside Laboratories, Inc.)

Chlorotrianisene for the synthetic estrogen tri-(*p*-anisyl)chloroethylene: Tace (The Wm. S. Merrell Company)

Cyanocobalamin for vitamin B_{12}

Iproniazid for 1-isonicotinyl-2-isopropyl hydrazine: Marsilid (Hoffmann-LaRoche, Inc.)

Isoniazid for isonicotinic acid hydrazid (isonicotinylhydrazine): Nydrazid (E. R. Squibb & Sons) and Niadrin (Endo Products, Inc.)

Neomycorsone for a mixture of neomycin sulfate and cortisone acetate: Neosone (The Upjohn Company)

Pentaerythritol Tetranitrate: Peritrate Tetranitrate (Chilcott Laboratories, Division of the Maltine Company)

Propylhexedrine for 1-cyclohexyl-2-methylaminopropane: Benzedrex (Smith, Kline & French Laboratories)

Testosterone Cyclopentylpropionate for testosterone beta-cyclopentylpropionate

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST. . . . . CHICAGO 10, ILL.
Edited by . . . . . AUSTIN SMITH, M.D.
Associate Editor . . . . . JOHNSON F. HAMMOND, M.D.
Editor for Medical Literature Abstracts . GEORGE HALPERIN, M.D.

Subscription price . . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

TREATMENT OF CANCER

The treatment of cancer, once limited to the use of surgery, x-rays, and radium, has been expanded considerably in recent years. New anticancer drugs have been developed, and hormones and radioactive isotopes have been applied to the therapy of malignant disease. These new agents represent valuable additions to the therapeutic program, but the optimistic publicity that has accompanied their use has tended to obscure several facts. In the first place, most of these substances have a relatively narrow range of therapeutic activity. The anticancer drugs, for example, are effective almost exclusively against the lymphomas, the sex steroids act only on a few types of carcinoma, and other substances are similarly limited in their action. Moreover, while these agents may prolong life and make it more comfortable, they are for the most part palliative rather than curative. Permanent cures are still achieved largely with surgery and/or external irradiation administered to patients with early lesions that have not yet metastasized widely. In spite of the many new techniques of treatment, most patients with advanced cancer still die of their disease. The search for truly curative anticancer agents with broad ranges of therapeutic activity continues, but, until such agents are found, surgery and irradiation remain the mainstays of therapy for most types of malignant lesions.

In cancer surgery, progress has been made along several fronts. More radical surgery, made practical by advances in anesthesiology, blood and electrolyte replacement, endocrine substitution, and control of infections, has expanded the concept of operability and made it possible to relieve symptoms and prolong life in many cases of cancer with extensive local spread. Total pneumonectomy for bronchogenic carcinoma, pelvic exenteration for advanced uterine, bladder, and rectal carcinoma, and radical resection of the mandible for carcinoma of the floor of the mouth are examples of this type of procedure. In general, surgical removal of metastatic lesions in distant organs has not proved effective, but in some cases apparent cure has followed the excision of solitary pulmonary lesions derived from uterine or rectal neoplasms, and removal of metastatic adenocarcinomas involving the central nervous system has been found to be a useful procedure. Many palliative operations have been developed for use when direct attack on a tumor is not possible. These include new and improved techniques for relief of malignant obstruction of the urinary, gastrointestinal, or biliary tracts, and operations designed to inhibit tumor growth by alteration of the hormone balance in patients with tumors of the breast and reproductive system. Castration and adrenalectomy are examples of the latter category. These procedures actually constitute an indirect form of chemical therapy.

The field of radiation therapy has also seen remarkable technical advances, many of them by-products of research on atomic energy. Although treatment was once limited to the use of medium voltage x-rays, radium, and radon, the radiotherapist now has at his disposal supervoltage x-ray generators, new types of radiation from the cyclotron, betatron, and other particle accelerators, and many new radioactive substances that can be applied to malignant lesions in a variety of ways. Unfortunately, clinical results have not been greatly improved by the application of these new techniques, although in some instances trial has been on too small a scale to permit final evaluation. Supervoltage (2,000 to 4,000 kv.) x-ray generators, with their increased depth dose per unit skin dose, have not given significantly better results in the treatment of deep-seated cancer than medium voltage (100 to 400 kv.) x-ray machines. The even more penetrating (10,000 to 70,000 kv.) x-rays that can be produced by the betatron have the practical disadvantage of a high skin dose at the point of exit of the beam from the body. It appears that the relative depth dose of x-rays can be increased more effectively and safely by modification of the technique of irradiation than by changes in the quality of the rays. Multiple field therapy, rotational therapy (rotation of the patient with the x-ray beam centered on the lesion), and the protection of the skin with grids or perforated shields have been effective in this regard. Among the newly available types of radiation produced by accelerators, the extremely high-energy, positively charged particles, notably protons, have shown the most promise in the treatment of deep lesions, because of the relatively low ionization that they produce at the surface of the body and the extremely dense ionization toward the end of their range. Neutron irradiation has not given results superior to those obtainable with x-rays. Neutron irradiation of tumors previously infiltrated with material that can be made radioactive by such bombardment is still in the experimental stage.

The use of radioactive isotopes has made the administration of radiation a much more flexible procedure but has not yielded types of radiation or biologic effects fundamentally different from those previously available. Radioactive isotopes in the form of solids, solutions, or colloidal suspensions may now be used not only topically and interstitially but also orally, intravenously, intraarterially, by instillation into body cavities, and at a distance from the body. These procedures often permit better localization of radiation than has heretofore been possible. Localization may be metabolic, as when systemically administered radioactive iodine (I^{131}) is localized in thyroid tissue, or it may be physical, as when intraperitoneally administered radioactive gold colloids are deposited on the surface of the peritoneum involved by neoplastic implants or are carried to regional nodes via the lymphatics. Immunological localization has been attempted by preparing radioactive organ-specific anti-

bodies, but none of these has been found useful in treatment. Mechanical localization can be achieved by infiltration of tissues with radioactive colloidal suspensions or by interstitial implantation of flexible wires or sutures containing radioactive substances such as cobalt 60 or gold 198. Effective irradiation of superficial lesions can be accomplished with surface applicators containing radioactive phosphorus or strontium, both of which give off beta rays free of penetrating gamma rays. Ruthenium 106 is also a useful source of beta rays. Gamma teletherapy is now possible with machines containing large quantities of radioactive cobalt, and units containing europium 152-154 or cesium 137 are being tested.

The chemical attack on cancer continues to be the subject of intensive research. This approach is based on the principle that the metabolic and mitotic activity of most neoplastic cells is greater than that of most normal cells and that this increased activity makes the neoplastic cell more susceptible to the cytotoxic action of radiation and many chemicals. The fact that some rapidly growing normal cells in the bone marrow and intestine are also damaged by these same agents indicates that the quantitative differential is not great. This, added to the fact that cancer cells, like bacteria, are capable of developing resistance to therapeutic agents, accounts for the many failures in the drug therapy of cancer. Qualitative metabolic differences in cancer cells that can be utilized in treatment have not been described.

Many anticancer drugs have been tested, but only a few have had wide clinical trial. Nitrogen mustards given intravenously have little effect on carcinomas but produce temporary remissions in a high percentage of patients with Hodgkin's disease, lymphatic leukemia, lymphosarcoma, giant follicular lymphoblastoma, and mycosis fungoides. Given intra-arterially, nitrogen mustard has produced local destruction of carcinoma of the tongue, lung, kidney, and other organs, but cures have not been obtained. Triethylene melamine (TEM) given orally or intravenously produces results similar to those obtained with nitrogen mustard in the lymphomas. Folic acid antagonists ("aminopterin" or "a-methopterin") are useful chiefly in acute leukemia of children. Urethan (ethyl carbamate) given orally produces clinical improvement in chronic leukemia, especially in the myelogenous variety.

Other, more questionable, treatments have been proposed. Fowler's solution (potassium arsenite) is effective particularly in Hodgkin's disease and chronic myelogenous leukemia, but treatment must be prolonged and the incidence of toxic manifestations is high. Stilbamidine (4,4′-stilbenedicarboxamidine) and related compounds produce symptomatic relief in multiple myeloma, but there is little objective improvement. A polysaccharide extracted from Serratia marcescens (Bacillus prodigiosus) produces hemorrhagic changes in animal tumors and occasionally a decrease in the size of lymphomatous or sarcomatous tumors in man, but it also produces fever and severe hypotension and is regarded as unpredictable and hazardous. Colchicine, resin of podophyllin, antireticular cytotoxic serum, K-R (an extract prepared from killed Trypanosoma cruzi), H. 11 (an extract of the urine of normal persons), and "krebiozen" are among the agents that have been advocated in some quarters but have not been generally accepted by experts in the cancer field.

Hormone therapy has been found beneficial only in certain kinds of cancer, and in these it is believed that the environment of the tumor rather than the tumor itself is affected. Estrogens produce regression of local and metastatic lesions in carcinoma of the prostate and may prolong life for many years. They are also of benefit in postmenopausal carcinoma of the breast and appear to have some effect on carcinoma of the bladder and chorioepithelioma. Androgens have a palliative effect in carcinoma of the breast with extensive metastasis. There is equivocal evidence that progesterone has value in carcinoma of the breast, cervix, and prostate. Cortisone and corticotropin have no consistent effect on the objective manifestations of carcinoma, but they do inhibit to some extent the growth of the malignant lymphomas. In the acute leukemias they produce spectacular remissions of short duration; in chronic leukemias the results are unpredictable, with aggravation of the disease sometimes occurring. The one feature of chronic leukemia that is regularly benefited, however, is the hypersplenic phase. When hemolytic, neutropenic, and thrombopenic crises occur, cortisone or corticotropin produces the same benefits as splenectomy, even when x-rays and other measures have failed to do so.

Other approaches to the therapy of cancer that have been employed experimentally include the use of viruses that selectively attack and destroy neoplastic cells, the attempt to stimulate immunity to cancer in the host by inoculation with extracts of tumor and other tissues, and the destruction of superficial tumors with ultrasonic waves. None of these approaches is yet of practical value in man.

In the current preoccupation with specific therapy, sight is often lost of the fact that the patient as well as the cancer must be treated. The patient's morale must be maintained, and general supportive treatment must be utilized. The relief of secondary infection with antibiotics, of disturbances in fluid, electrolyte, and nutritional balance with parenteral fluids, of any associated congestive heart failure with standard remedies, and of anemia with transfusions will often do more to make the patient comfortable than any specific measures available. It should be noted, however, that iron therapy has no value except in the treatment of hypochromic anemia following hemorrhage. Liver extract and supplementary vitamin B_{12} are equally valueless unless there is a specific deficiency of these substances.

The solution to the problem of specific anticancer therapy awaits a better understanding not only of the metabolism of cancer cells but of the mechanism of normal growth as well. For the acquisition of this knowledge unrestricted basic research may well be as important as "project" or restricted research. Support and coordination of research is being provided in the United States on an unprecedented scale by such organizations as the American Cancer Society, the American Association for Cancer Research, the National Cancer Institute, the Atomic Energy Commission, the Committee on Growth of the National Research Council, and the Committee on Research of the A. M. A.'s Council on Pharmacy and

Chemistry. An example of the type of activity sponsored by the last-named committee is the continuing cooperative study on the use of steroid hormones in the treatment of advanced breast, thyroid, and genitourinary carcinoma. The results of the breast carcinoma study, in which 45 clinics and 14 pharmaceutical firms participated, have been published in THE JOURNAL.[1]

The development of improved methods of cancer therapy seems certain. In the meantime, over-optimism concerning new remedies must be guarded against assiduously. Every effort must be made on the part of scientists, science writers, and pharmaceutical manufacturers to prevent the release to the lay press of overenthusiastic news stories of new "wonder drugs" or therapeutic procedures. The false hopes raised by such stories have caused patients to postpone urgent surgery or to refuse irradiation until their lesions have advanced beyond all hope of control. Persons in high government office and other responsible positions also have an obligation to the public to refrain from promoting new and inadequately tested therapeutic measures. Such misguided activity can result in incalculable harm to the health of the public.

1951 EXPENDITURES FOR MEDICAL CARE

The Bureau of Medical Economic Research has recently published another item in its series on personal consumer expenditures for medical care.[1] The basic data are from the July, 1952, issue of the *Survey of Current Business,* United States Department of Commerce. New data are given for 1951 and some slight revisions of the previously published data for 1949 and 1950.

Briefly stated, the percentages of total personal consumer expenditures spent for medical care and for each of the major items of medical care were about the same in 1951 as they were in 1950. The percentage spent for medical care was 4.3% in 1951 and 4.3%, according to the revised data, for 1949 and 1950. The percentages spent for the services of physicians and of hospitals continue to be 1.2 and 1.0 respectively. The percentage of the medical care dollar spent on physicians' services in 1951 was 28.1, as compared with 28.3 in 1950 and 28.9 in 1949 according to the revised data for the two earlier years. On the other hand, the share of the medical care dollar going to hospitals reached an all-time high of 23.8% in 1951 and the revised data indicate 22.0% for 1949 and 23.4% for 1950. The dentists' share of the medical care dollar was 11.9% in 1949, 11.5% in 1950, and 11.0% in 1951.

Personal consumer expenditures for medical care rose from 7.8 billion dollars in 1949 to 8.4 billion dollars in 1950 to 9.0 billion dollars in 1951. Total personal consumer expenditures for all goods and services, however, rose slightly faster, from 180.6 billion dollars in 1949 to 194.3 billion dollars in 1950 to 208.0 billion dollars in 1951. Thus the American people continue to devote only slightly more than 4% of their total consumer expenditures to medical care items, among which hospital care bulks larger and larger.

GENERAL PRACTITIONER AWARD

The General Practitioner Award was presented for the first time in January, 1948, at the Association's meeting in Cleveland. Since then it has been awarded annually at the midyear session. It has been the practice for the Board of Trustees to select three names from those submitted by the state societies and present them to the House of Delegates for its choice. At its meeting in Chicago in June, 1952, the House approved the following communication from the Board of Trustees:

> It is believed that a much more dignified and fair approach would be to have the Chairman of the Board appoint an impartial committee, to remain anonymous until after the award is made, which would study the credentials and choose from the nominations submitted the general practitioner most qualified for the honor.

To meet the wishes of the House, biographical material submitted by various state medical societies for the General Practitioner Award should be in the office of the Secretary of the American Medical Association no later than Nov. 1.

SCIENTIFIC EXHIBIT, DENVER SESSION

The Scientific Exhibit will again be one of the features of the Clinical Session in Denver, Dec. 2 to 5, 1952. All activities of the session, except the House of Delegates, will be housed in the remodeled and enlarged Municipal Auditorium. The Scientific Exhibit will be located on the ground floor of the auditorium, together with facilities for colored television, motion pictures, and several of the meeting rooms.

Application blanks are now available for space in the Scientific Exhibit, and prospective authors of exhibits should make application as soon as possible. Attention is called to the fact that the Denver Session is a clinical meeting and hence emphasis is placed largely on the clinical aspects of medicine rather than on research activities.

The Committee on Scientific Exhibit is composed of three members of the Board of Trustees: L. W. Larson, M.D., Bismarck, N. D., chairman; Thomas P. Murdock, M.D., Meriden, Conn.; and James R. McVay, M.D., Kansas City, Mo. The subcommittee on Scientific Exhibit in Denver includes Dumont H. Clark, M.D., chairman; Thomas M. Van Berger, M.D.; and Marvin E. Johnson, M.D.

Application blanks for space may be obtained from the Director, Scientific Exhibit, American Medical Association, 535 N. Dearborn St., Chicago 10.

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1. Estrogens and Androgens in Mammary Cancer, Report to the Council on Pharmacy and Chemistry, J. A. M. A. **140:** 1214 (Aug. 13) 1949. Proceedings of the First Conference on Steroid Hormones and Mammary Cancer, Chicago, A. M. A. (April) 1949. Current Status of Hormone Therapy of Advanced Mammary Cancer, Report to the Council on Pharmacy and Chemistry, ibid. **146:** 471 (June 2) 1951. Lazlo, D., and others: Effect of Testosterone on Patients with Bone Metastases: A Metabolic Study, Particularly of Breast Carcinoma, Report to the Council on Pharmacy and Chemistry, ibid. **148:** 1502 (April 26) 1952.

1. Dickinson, F. G.: 1951 Expenditures for Medical Care, Publication M-69, Chicago, American Medical Association, 1952. The latest item in this series had been Medical Care Expenditures, Prices and Quantity, 1930-1950, J. A. M. A. **147:** 1354-1359 (Dec. 1) 1951, which was reprinted as Bulletin 87. Publication M-69 is really a small supplement to Bulletin 87. A copy of these two publications may be obtained from the Bureau of Medical Economic Research, American Medical Association, 535 N. Dearborn St., Chicago 10.

MEDICAL NEWS

CALIFORNIA

Warning—Epidemic Encephalitis.—Dr. Wilton L. Halverson, state director of public health, has issued a warning that encephalitis may become epidemic in the Central Valley of California this year unless intensified action against the mosquito that transmits the disease is taken by control agencies and individual householders alike. The threat of a mosquito-borne epidemic is indicated in reports of both human and equine cases of encephalitis in the San Joaquin Valley, coupled with the appearance of extremely large numbers of Culex tarsalis mosquitoes.

At a meeting of representatives of the vector control advisory committee, State Department of Public Health, and representatives of mosquito abatement districts in the Central Valley, preventive and remedial measures were suggested. Individual householders were urged to eliminate mosquito breeding sources around their premises, keep adult mosquitoes out of the house by careful screening of doors and windows, and use hand sprays or aerosol bombs to kill mosquitoes getting indoors. All persons, and particularly children, were advised to remain indoors as much as possible during evening hours, when Culex tarsalis usually attacks, and to use mosquito repellents when outdoors.

Health departments were asked to be on the alert, maintaining close contact with private physicians, in order to provide an up-to-the-minute statewide picture, with the earliest possible warning of epidemic conditions. Encephalitis cases in the high-prevalence areas of the Central Valley normally reach a peak in July, August, and September. Mosquito abatement districts were urged to intensify their control measures directed specifically at the Culex tarsalis species, and irrigation districts and individual ranchers were asked to support the control measures, giving particular attention to irrigation practices to prevent unnecessary standing water, which would create mosquito breeding places.

ILLINOIS

Health at the State Fair.—Many phases of health are emphasized at the Illinois Centennial State Fair, which is being held at Springfield Aug. 8-17. In addition to displays of health subjects throughout the fairgrounds, free movies, and dental and chest x-ray examinations are provided. Inside the Illinois Building are displayed improvements in sanitation during the past 100 years. As part of the tuberculosis case finding program, the State Department of Public Health, in cooperation with the Illinois Tuberculosis Association, is offering x-ray examinations of the chest. The Department of Public Health is also sponsoring a special "health tent" with exhibits and motion pictures on many health subjects.

Chicago

Fellowship in Pediatric Cardiology.—The Children's Division of Cook County Hospital in Chicago has an opening for a fellow in pediatric cardiology. Training in angiocardiography and catheterization will be available if desired. Information may be obtained from Dr. Benjamin M. Gasul, 700 S. Wood St., Cook County Children's Hospital, Chicago.

Dr. MacEachern Honored.—Dr. Malcom T. MacEachern, director of professional relations for the American Hospital Association, was presented with a badge bearing the coat of arms of the Comité des Hôpitaux du Quebec (the Committee of Catholic Hospitals of Quebec) and a citation in recognition of his work in the hospital field, during the session of the Comité in Quebec City, June 23-25. In July Dr. MacEachern was in Brazil, South America, where he gave a three week lecture course to students in hospital administration at the University of São Paulo. While in Brazil he also participated in an Institute for Hospital Administrators and served as consultant on local, regional, state, and national organization of hospitals. The trip was arranged under the auspices of the University of São Paulo.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

IOWA

State Medical Society Election.—At its meeting in Des Moines, April 27-30, the Iowa State Medical Society elected Dr. Ben T. Whitaker, Boone, president; Dr. Robert N. Larimer, Sioux City, president-elect; Dr. Elias B. Howell, Ottumwa, first vice-president; Dr. Lester C. Kern, Waverly, second vice-president; Dr. Allan B. Phillips, Des Moines, secretary; and Dr. N. Boyd Anderson, Des Moines, treasurer.

Dr. Barnes Retires from Faculty.—Dr. Milford E. Barnes, since 1930 head of the department of hygiene and preventive medicine, University of Iowa, was honored at a testimonial dinner June 4. Dr. Barnes, whose retirement from the university faculty was recently announced, has served as director of the university's department of health since 1930; and since 1943 he has been consulting director of the Iowa State Hygiene Laboratory, which he served as director for many years.

Before coming to the university he was a field director under the international health division of the Rockefeller Foundation. A wrist watch and a morocco-bound book, containing more than 100 letters from former students and co-workers, was presented to Dr. Barnes. Greetings from individual friends, societies, and organizations in various countries were read.

MINNESOTA

Dr. Buie Receives Alumni Award.—Dr. Louis A. Buie, professor of surgery in the Mayo Foundation, University of Minnesota, Rochester, has been given the 1952 Alumni Honor Award and Gold Key by the Medical Alumni Association of the University of Maryland "for outstanding contributions to medicine and distinguished service to mankind." The presentation was made June 5, when Dr. Buie addressed the association on "The Fruit of Loyal Nature and of Noble Mind."

Before becoming chief of the department of proctology at the Mayo Clinic in 1919, Dr. Buie was affiliated with the University of Maryland hospital and James Lawrence Kernan Hospital and Industrial School for Crippled Children in Baltimore. He is a past president of the American Proctologic Society, secretary of the American Board of Proctology, chairman of the Council on the Constitution and By-Laws of the American Medical Association, and a member of the Judicial Council of the Association and the Committee on Education and Publications of the National Foundation for Infantile Paralysis, Inc.

NEW YORK

Genesee County Sesquicentennial.—Medicine played a prominent part in the week-long observance of Genesee County's Sesquicentennial celebration through the activities of the Genesee County Medical Society and the Woman's Auxiliary of the Genesee Memorial Hospital. The medical group had a float in the Batavia parade portraying the advance of medicine since the founding of Genesee County 150 years ago. Dr. Charles M. Graney, Batavia, was chairman of the County Medical Society's Exhibition Committee; Dr. Alfred L. George, Batavia, wrote and directed the pageant, which had a cast of 500 characters.

New York City

Dr. Wolf Appointed Dean in Vermont.—Dr. George A. Wolf Jr., director of the outpatient department of New York Hospital and assistant professor of clinical medicine at Cornell Medical College, has been appointed dean of the college of medicine of the University of Vermont, Burlington, and professor of clinical medicine. He succeeds Dr. William E. Brown, who retired June 30.

Report on Tuberculosis.—In its annual report for the 50th year of an organized drive against tuberculosis, the New York Tuberculosis and Health Association points out that though fewer persons are dying of the disease today, the incidence continues at an alarmingly high level and out of proportion to the medical and social progress of the last half century. During the last 20 years the incidence has not materially changed: there were 17,645 cases of pulmonary tuberculosis in New York at the end of 1931 as compared to 17,911 cases on Dec. 31, 1951. A slow but steady increase of cases has marked the last five years. Of the 13 city hospitals caring for tuberculosis patients, 6 have more than 100% bed occupancy; 85% of capacity is the normal hospital occupancy, but according to the report none of the 13 operates at this figure.

OKLAHOMA

Insurance Company Cancels Malpractice Policy.—The London and Lancashire Indemnity Company of Hartford, Conn., has cancelled the master policy held with the Oklahoma State Medical Association for the writing of malpractice insurance for its members. The company stated that it was withdrawing from this field of insurance. Physicians whose malpractice insurance was with the London and Lancashire will find it necessary to place this coverage with companies that are now writing it in Oklahoma. The insurance committee of the association is attempting to negotiate a new contract with another company. Over 985 members of the association held contracts with the London and Lancashire.

PENNSYLVANIA

100 Years of Pennsylvania Medicine.—"A Century of Medicine, 1848-1948," a history of medicine in the Commonwealth of Pennsylvania, has just been published by the State Medical Society. Among the medical "firsts" in this country, which it lists for Pennsylvania, are the following: the first general hospital, first permanent medical periodical, and the first board of health. The first woman's medical school in the world was established in Philadelphia more than a century ago. The Medical Society of the State of Pennsylvania was the 16th state society to be organized, coming into being one year after the founding of the American Medical Association.

Philadelphia

Antivirus Research.—Schenley Laboratories, Inc., Lawrenceburg, Ind., has announced a grant of $17,000 to the Langbord Virus Laboratory at Hahnemann Medical College and Hospital, for antivirus research. The studies will be made by Dr. Bernard A. Briody, Ph.D., director of the virus laboratory.

Dr. Long Appointed to UNESCO Commission.—Dr. Esmond Ray Long was recently appointed a member of the U. S. National Commission of UNESCO, as representative of the National Academy of Sciences, National Research Council. He succeeds Detlev W. Bronk, Ph.D., president of Johns Hopkins University, Baltimore.

Director of the Henry Phipps Institute for Study, Treatment and Prevention of Tuberculosis, Dr. Long served as chief consultant on tuberculosis to the Surgeon General's Office, U. S. Army, during World War II, and later directed the tuberculosis section of public health in the U. S. zone in Germany. He has served as president of the National Tuberculosis Association, American Association of Pathologists and Bacteriologists, and the American Association of the History of Medicine.

SOUTH CAROLINA

Man of the Year.—Dr. Walter R. Mead, Florence, was the recipient recently of the "Man of the Year" civic service award, sponsored annually by the Rotary, Kiwanis, Optimist, Lions, and Exchange clubs of Florence.

Cancer Award.—Dr. Thomas A. Pitts, chairman of the Board of Trustees of the Medical College of the State of South Carolina, Charleston, was awarded the medal of the American Cancer Society for outstanding service in the cancer program for 1951. The citation was made by the South Carolina Division of the American Cancer Society, "in recognition of distinguished service in the control of cancer." He has been director of the South Carolina Baptist Hospital Cancer Clinic since it was organized and has also directed a cancer detection clinic there for the past four or five years.

VIRGINIA

Dr. Caudill Honored.—Dr. Walter Cleveland Caudill of Pearisburg was recently honored by his alma mater, the Medical College of Virginia in Richmond, which conferred on him the honorary degree of master of science in general medicine. Dr. Caudill was president of the Medical Society of Virginia (1950-1951), and in 1951 the House of Delegates of the Medical Society of Virginia selected him as "General Practitioner of the Year." For several years he has served in the Virginia State Legislature.

WISCONSIN

Health Day for Business Executives.—On July 30 the University of Wisconsin Industrial Management Institute sponsored an executive leadership program for business men. The faculty of the University of Wisconsin Medical School, Madison, cooperated in providing information on the symptoms of coronary thrombosis, nervous disorders, cancer, and tuberculosis. Dr. John W. Brown, director of the university's department of student health, who was in charge of the health day program, stated that the program was planned "to help the group understand how medical men diagnose and treat ailments that are especially prevalent among businessmen . . . to make available to business executives the most advanced scientific knowledge that will help lengthen their lives."

GENERAL

Dates Changed for Graduate Course in Urology.—The American Urological Association announces that the postgraduate course in urology, known as the South Central Section Seminar, which was scheduled to be given in Kansas City, Mo., Dec. 14-18 (THE JOURNAL, June 14, p. 698), will be given instead in the same city on Jan. 11-14, 1953. Information may be obtained from the headquarters of the association, 102-110 Second Ave., S.W., Rochester, Minn.

Proposed Nation-Wide Medical Code for Boxing.—Measures designed to protect young boxers and to promote the exchange of information on the medical effects of athletics were discussed at a symposium July 27 in New York, under the sponsorship of the State Athletic Commission. Dr. Marvin A. Stevens, New York, member of the Medical Advisory Board of the commission, was chairman.

A plea for establishing national standards to protect boxers was made by Dr. Frank R. Ferlaino, New York, former director, State Athletic Commission's medical advisory board. Among the steps suggested by Dr. Ferlaino were the establishment of a national medical sports association for interchanging information, recognized medical criteria for stopping bouts, standardized medical equipment, and safer gloves, mats, and mouthpieces for boxers. The National Boxing Association will hold a meeting on the Medical Aspects of Boxing in Montreal, Canada, Sept. 8-10.

Dermatologists Meet in San Francisco.—The Pacific Dermatologic Association will meet in San Francisco Aug. 29-30 under the presidency of Dr. Nelson P. Anderson, Los Angeles. On Friday the sessions at the Palace Hotel will open with the presidential address at 9 a. m., which will be followed at 9:20 by a talk on "The Diagnostic Pitfalls in Dermal Pathology" by Dr. Marcus R. Caro of Chicago, clinical professor of dermatology, University of Illinois. Brief reports of scientific activities will be given by the universities of Colorado, Utah, Washington, Oregon, Southern California, California at Los Angeles, and California, Stanford University, and the College of Medical Evangelists.

The Saturday session, which will be held in the Letterman Army Hospital, will open at 9 a. m. with a demonstration of clinical techniques. At 10:30 a. m. there will be a report from the International College of Dermatology in London under the chairmanship of Dr. Norman N. Epstein of San Francisco.

Discussion roundtable groups will be held during the luncheon at the hospital, which will be followed by a clinical meeting of the hospital.

On Sunday at 9 a. m. there will be a seminar in histopathology at Letterman Army Hospital.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States and its territories and possessions in the weeks ended as indicated:

Area	July 19, 1952	July 12, 1952	July 21, 1951
New England States			
Maine	1	3	2
New Hampshire	..	..	1
Vermont	1	1	1
Massachusetts	3	6	17
Rhode Island	..	..	..
Connecticut	6	2	9
Middle Atlantic States			
New York	68	26	52
New Jersey	16	10	9
Pennsylvania	18	8	16
East North Central States			
Ohio	69	41	26
Indiana	19	5	8
Illinois	46	33	52
Michigan	56	19	37
Wisconsin	26	5	29
West North Central States			
Minnesota	27	17	6
Iowa	82	72	17
Missouri	13	5	6
North Dakota	..	..	1
South Dakota	15	15	1
Nebraska	55	35	9
Kansas	37	19	9
South Atlantic States			
Delaware	3	..	..
Maryland	7	2	2
District of Columbia	1	5	..
Virginia	17	13	9
West Virginia	22	17	2
North Carolina	14	11	4
South Carolina	1	..	4
Georgia	25	18	34
Florida	22	38	17
East South Central States			
Kentucky	73	18	12
Tennessee	24	21	21
Alabama	20	13	31
Mississippi	51	38	42
West South Central States			
Arkansas	14	9	19
Louisiana	83	60	41
Oklahoma	46	47	21
Texas	243	296	66
Mountain States			
Montana	6	5	1
Idaho	4	3	3
Wyoming	1	1	8
Colorado	10	10	43
New Mexico	19	22	1
Arizona	8	7	7
Utah	4	..	19
Nevada	..	..	..
Pacific States			
Washington	38	18	5
Oregon	19	7	4
California	59	46	70
Territories and Possessions			
Alaska	..	..	4
Hawaii	12	11	..
Puerto Rico	1	2	..
Total	1,405	1,060	798

During the "disease year," which began with the week ended July 5, a total of 5,406 cases of poliomyelitis had been reported (week ended July 19) as compared with 3,351 for the same period in 1951; in 1949, the corresponding figure was 5,313.

FOREIGN

Congress of Therapeutics.—The International Congress of Therapeutics will be held in Madrid, Spain, Oct. 16-18. The main topics for discussion will be potassium, massive hormonotherapy, and radioisotopes. Among the speakers will be Paul F. Hahn, Ph.D., Nashville, Tenn., who will discuss "Tumor Therapy by Radioisotopes."

LATIN AMERICA

Dr. Kemeny Honored.—Dr. Esteban Kemeny, director of the School of Dietetics, Santiago, Chile, has been elected president of the Nutrition Society of Chile. He recently visited the United States under the sponsorship of the Institute of Inter-American Affairs for the purpose of observing American dietetic methods.

CORRECTION

Annual License Renewal Not Required in Florida.—On page 506 of the May 31, 1952, JOURNAL under the heading "Annual Registration" is a statement to the effect that a new Florida law requires annual renewal of licenses of practitioners of medicine. Annual renewal is not required. The statement should have been to the effect that the Florida law requires annual registration of such licenses with the state board of health.

MEETINGS

AMERICAN MEDICAL ASSOCIATION PUBLIC RELATIONS INSTITUTE, Edgewater Beach Hotel, Chicago, Sept. 4-5. Mr. Leo E. Brown, 535 N. Dearborn St., Chicago 10, Director.

ALASKA TERRITORIAL MEDICAL ASSOCIATION, Anchorage, Aug. 21-23. Dr. William P. Blanton, P. O. Box 2569, Juneau, Secretary.

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS, The Homestead, Hot Springs, Va., Sept. 4-6. Dr. William F. Mengert, 2211 Oak Lawn Ave., Dallas, Texas, Secretary.

AMERICAN COLLEGE OF SURGEONS, Waldorf-Astoria, New York, Sept. 22-26. Dr. Michael L. Mason, 40 East Erie St., Chicago 11, Secretary.

AMERICAN CONGRESS OF PHYSICAL MEDICINE, Roosevelt Hotel, New York, Aug. 25-29. Dr. Frances Baker, One Tilton Ave., San Mateo, Calif., Secretary.

AMERICAN HOSPITAL ASSOCIATION, Philadelphia, Sept. 15-18. Mr. George Bugbee, 18 East Division St., Chicago 10, Executive Director

AMERICAN MEDICAL WRITERS' ASSOCIATION, Jefferson Hotel, St. Louis, Oct. 1. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

AMERICAN PHYSIOLOGICAL SOCETY, New Orleans, Sept. 4-6. Dr. E. F. Adolph, University of Rochester School of Medicine and Dentistry, Rochester, N. Y., Secretary.

AMERICAN ROENTGEN RAY SOCIETY, Shamrock Hotel, Houston, Texas, Sept. 23-26. Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Secretary.

AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS, Hotel del Coronado, San Diego, Calif., Sept. 10-13. Dr. Casper M. Epsteen, 25 East Washington St., Chicago 2, Secretary.

ANNUAL GULF COAST REGIONAL CONFERENCE ON INDUSTRIAL HEALTH, Rice Hotel, Houston, Tex., Sept. 24-27. Dr. W. H. Hamrick, P. O. Box 2371, Houston, Tex., Chairman.

BIOLOGICAL PHOTOGRAPHIC ASSOCIATION, Hotel New Yorker, New York, Sept. 10-12. Mr. Lloyd E. Varden, Pavelle Color, Inc., 533 W. 57th St., New York 19, Secretary.

COLORADO STATE MEDICAL SOCIETY, Stanley Hotel, Estes Park, Sept. 9-12. Mr. Harvey T. Sethman, 835 Republic Bldg., Denver 2, Executive Secretary.

CONSTANTINIAN SOCIETY, Lake Placid Club, Lake Placid, N. Y., Oct. 1-4. Dr. C. F. Shook, P. O. Box 1035-36, Toledo 1, Ohio, Secretary.

MEDICAL SOCIETY OF DELAWARE, Rehoboth, Sept. 8-10. Dr. Andrew M. Gehret, 822 North American Bldg., Wilmington, Secretary.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, Hotel Statler, Washington, Sept. 29-Oct. 1. Mr. Theodore Wiprud, 1718 M St. N.W., Washington, Secretary.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, Bellevue-Stratford Hotel, Philadelphia, Sept. 28-Oct. 2. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh 22, Secretary.

MEDICAL SOCIETY OF VIRGINIA, Jefferson Hotel, Richmond, Sept. 28- Oct. 1. Mr. Robert L. Howard, 1105 West Franklin St., Richmond, Executive Secretary.

MICHIGAN STATE MEDICAL SOCIETY, Book-Cadillac Hotel, Detroit, Sept. 24-26. Dr. L. Fernald Foster, 606 Townsend St., Lansing 15, Secretary.

MISSISSIPPI VALLEY MEDICAL SOCIETY, Jefferson Hotel, St. Louis, Oct. 1-3. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

MONTANA MEDICAL ASSOCIATION, Florence Hotel, Missoula, Sept. 18-21. Mr. L. R. Hegland, 104 North Broadway, Billings, Executive Secretary.

NATIONAL MEDICAL ASSOCIATION, Chicago, Aug. 11-15. Dr. John T. Givens, 1108 Church St., Norfolk 10, Va., General Secretary.

NEUROSURGICAL SOCIETY OF AMERICA, The Cloister, Sea Island, Ga., Sept. 18-20. Dr. C. D. Hawkes, 22 North Manassas St., Memphis 5, Tenn., Secretary.

NEVADA STATE MEDICAL ASSOCIATION, Reno, Aug. 21-23. Dr William A. O'Brien III, 505 Chestnut St., Reno, Secretary.

NEW HAMPSHIRE MEDICAL SOCIETY, Mt. Washington Hotel, Bretton Woods, Sept. 7-9. Dr. Deering G. Smith, 44 Chester St., Nashua, Secretary.

NORTH PACIFIC PEDIATRIC SOCIETY, Challenger Inn, Sun Valley, Idaho, Sept. 19-20. Dr. S. Gorham Babson, 1107 S.W. 13th Ave., Portland 5, Ore., Secretary.

NORTH PACIFIC SOCIETY OF INTERNAL MEDICINE, Sun Valley, Idaho, Sept. 19-20. Dr. Robert L. King, 1115 Terry Ave., Seattle 1, Wash., Secretary.

NORTH TEXAS-SOUTHERN OKLAHOMA FALL CLINICAL CONFERENCE, Wichita Falls, Texas, Sept. 17. Dr. E. Aubrey Cox, Hamilton Bldg., Wichita Falls, Texas, Chairman.

PIEDMONT PROCTOLOGIC SOCIETY, Savannah Beach, Ga., Aug. 23. Dr. B. Richard Jackson, 224 Hillsboro St., Raleigh, N. C., Secretary.

RENO SURGICAL SOCIETY CONFERENCE, Reno, Nevada, Aug. 21-23. Dr. Olin C. Moulton, 130 N. Virginia St., Reno, Nevada, Chairman.

TRI-STATE MEDICAL SOCIETY OF TEXAS, LOUISIANA AND ARKANSAS, Texarkana, Texas, Oct. 2-3. Dr. Albert M. Hand, 619 Main St., Texarkana, Texas, Secretary.

U. S. CHAPTER, INTERNATIONAL COLLEGE OF SURGEONS, Conrad Hilton Hotel, Chicago, Sept. 2-5. Dr. Arnold S. Jackson, 1516 Lake Shore Drive, Chicago, Executive Secretary.

UTAH STATE MEDICAL ASSOCIATION, Salt Lake City, Sept. 4-6. Dr. T. C. Weggeland, 42 S. Fifth East St., Salt Lake City, Secretary.

VERMONT STATE MEDICAL SOCIETY, Mt. Washington Hotel, Bretton Woods, N. H., Sept. 7-9. Dr. James P. Hammond, 128 Merchants Row, Rutland, Secretary.

WASHINGTON STATE MEDICAL ASSOCIATION, Olympic Hotel, Seattle, Sept. 13-17. Dr. Bruce Zimmerman, 338 White-Henry-Stuart Bldg., Seattle, Secretary.

INTERNATIONAL

AERO MEDICAL ASSOCIATION INTERIM MEETING, Paris, France, Sept. 26-28. Dr. Armand Robert, 2 Rue Marbeuf, Paris 8e, France, Secretary.

AMERICAN CONGRESS OF INDUSTRIAL MEDICINE, Rio de Janeiro, Brazil, Sept. 20-28. Prof. Dr. Jose Pedro Reggi, Calle Arenales No. 981 Buenos Aires, Argentina, Director General.

AUSTRALASIAN MEDICAL CONGRESS, Melbourne Victoria, Australia, Aug. 22-30. Dr. C. H. Dickson, Medical Society Hall, 426 Albert St., East Melbourne, Victoria, Australia, General Secretary.

CONGRESS OF INTERNATIONAL INSTITUTE OF EMBRYOLOGY, University of Utrecht, Zoological Laboratory, Utrecht, Netherlands, Aug. 27-31. Dr. M. W. Woerdeman, Amsterdam, Holland, President.

EUROPEAN CONGRESS OF CARDIOLOGY, University of London, Bloomsbury, W.C.1, England, Sept. 10-12. Dr. K. Shirley Smith, 35 Wimpole St., London, W.1, England, Secretary.

EUROPEAN SOCIETY OF CARDIOVASCULAR SURGERY, Strasbourg, France, Oct. 3-4. Sir James Learmonth, Department of Surgery, University New Buildings, Edinburgh 8, Scotland.

INTERAMERICAN CARDIOLOGICAL CONGRESS, Buenos Aires, Argentina, Aug. 31-Sept. 7. Dr. Blas Moia, Larrea 1132, Buenos Aires, Argentina, Secretary-General.

INTER-AMERICAN CONGRESS OF PUBLIC HEALTH, Havana, Cuba. Sept. 26-Oct. 1. Pan-American Sanitary Bureau, 2001 Connecticut Ave., Washington, D. C.

INTER-AMERICAN CONGRESS OF RADIOLOGY, Mexico City, Mexico, Nov. 2-8. Dr. Guido Torres Martinez, Marsella No. 11, Mexico, D.F., Secretary-General.

INTERNATIONAL CONGRESS OF ANTHROPOLOGY AND ETHNOLOGY, Vienna, Austria, Sept. 1-8. For information write: Secretaries, Royal Anthropological Institute, 52 Upper Bedford Place, London, W.C.1, England.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Rio de Janeiro, Brazil, Aug. 24-30. Mr. Murray Kornfeld, 112 East Chestnut St., Chicago 11, Illinois, Executive Secretary.

INTERNATIONAL CONGRESS OF HAEMATOLOGY, Mar del Plata, Argentina, Sept. 21-26. Dr. Carlos Reussi, Anchorena 1710, Buenos Aires, Argentina, Secretary.

INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE, Nice-Cannes, France, and Monaco, Sept. 8-14. Dr. F. A. Sondervorst, 124 Avenue des Allies, Louvain, Belgium, Secretary-General.

INTERNATIONAL CONGRESS ON HYDATID DISEASE, Santiago, Chile, Nov. 21-24. Organizing Committee, P. O. Box 9183, Santiago, Chile.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Friends House, London, N.W.1, Eng. Sept. 15-18. Sir Harold Boldero, 12 Pall Mall East, London, S.W.1, England, Secretary.

INTERNATIONAL CONGRESS OF MEDICAL PRESS, Venice, Italy, Oct. 4-5. Dr. Bruno de Biasio, S. Marco 4646, Venice, Italy, Secretary.

INTERNATIONAL CONGRESS ON MEDICAL RECORDS, London, England, Sept. 7-12. Miss Gwen Perkins, 120 C Street S.E., Washington, D. C., Chairman.

INTERNATIONAL CONGRESS OF MILITARY MEDICINE AND PHARMACY, Montevideo, Uruguay, March 1-7, 1953. Dirreccion General del Servico de Sanitad Militar, 8 de Octubre y Mariano Moreno, Montevideo, Uruguay, Secretariat of the Congress.

INTERNATIONAL CONGRESS ON NEUROPATHOLOGY, Rome, Italy, Sept. 8-13. Dr. Armando Ferraro, 722 W. 168th St., New York, N. Y., U. S. A., Secretary General.

INTERNATIONAL CONGRESS OF OTORHINOLARYNGOLOGY, Amsterdam, Netherlands, June 8-15, 1953. Dr. W. H. Struben, J. J. Viottastraat 1, Amsterdam, Netherlands, Secretary.

INTERNATIONAL CONGRESS OF RADIOLOGY, Copenhagen, Denmark, July 19-25, 1953. Professor Flemming Norgaard, 10 Oster Voldgade, Copenhagen K., Denmark, Secretary General.

INTERNATIONAL CONGRESS OF THERAPEUTICS, Madrid, Spain, Oct. 16-18. Professor Armijo, Instituto de Farmacologia, Cuidad Universitaria, Madrid, Spain, Secretary.

INTERNATIONAL CONGRESS OF UROLOGY, The Waldorf-Astoria, New York, N. Y., U. S. A., Sept. 15-18. Dr. John A. Taylor, 2 East 54th St., New York, N. Y., U. S. A., Secretary-General.

INTERNATIONAL HOSPITAL CONGRESS, London, England, May 25-30, 1953. Capt. J. E. Stone, 10 Old Jewry, London, EC2, England, Hon. Secretary.

INTERNATIONAL STUDY CONFERENCE ON CHILD WELFARE, Bombay, India, Dec. 5-12. For information write: All India Save the Children Committee, 5 Carmichael Road, Bombay, India.

INTERNATIONAL UNION AGAINST TUBERCULOSIS, Rio de Janeiro, Brazil, Aug. 24-27. Prof. Etienne Bernard, 66 Blvd. St. Michel, Paris 6e, France, Secretary-General.

MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION, Vichy, France, Sept. 12-16. Dr. Margaret M. Wurts, 27 East Wellesley Road, Montclair, N. J., U. S. A., National Secretary.

NEURORADIOLOGICAL SYMPOSIUM, Stockholm, Sweden, Sept. 17-20. Docent Ake Lindbom, Symposium Neuroradiologicum, Serafimerlasarettet, Stockholm K., Sweden, Secretary.

PAN AMERICAN CONGRESS OF THE MEDICAL PRESS, Buenos Aires, Argentine, July 12-16, 1953. Secretaria del Congress, 763 Uriburu, Buenos Aires, Argentine.

WORLD CONGRESS OF JEWISH PHYSICIANS, Jerusalem, Israel, Aug. 10-14. Secretariat: % Israel Medical Association, Rehov Mesilat Yesharim, Beth Kovatz, Jerusalem, Israel.

WORLD CONGRESS OF MEDICINE, Montecatini, Italy, Oct. 16-18. Secretariat: Corso Trieste, 65, Rome, Italy.

WORLD FEDERATION OF MENTAL HEALTH, Brussels, Belgium, Aug. 25-Sept. 1. Dr. J. R. Rees, 19 Manchester St., London, W.1, England, Secretary.

WORLD MEDICAL ASSOCIATION, Athens, Greece, Oct. 12-16. Dr. Louis H. Bauer, 2 East 103d St., New York 29, N. Y., Secretary General.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Part I*, Sept. 8-10. All centers where there are five or more candidates. Exec. Sec., Dr. John P. Hubbard, 225 S. 15th St., Philadelphia 2.

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral.* Swampscott, Mass., Sept. 28-Oct. 1. Sec., Dr. C. B. Hickcox, 80 Seymour St., Hartford 15.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: *Written.* Various Centers, September 1953. Final date for filing applications was May 1. All candidates are now required to take the written examination. *Oral.* Philadelphia, October 1953. Ex. Sec., Miss Janet Newkirk, 66 East 66th St., New York 21.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Various centers and overseas, Oct. 20. Closing date for the acceptance of applications for the written examination was May 1. *Oral.* San Francisco, Sept. 3-6; Philadelphia, Nov. 13-14 and Washington, D. C., Nov. 17-18. Exec. Sec.-Treas., Dr. William A. Werrell, 1 West Main Street, Madison 3.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Written.* New Haven, Sept. 19-21. *Oral.* Chicago, May or June 1953. Final date for filing application for the oral examination is Jan. 15, 1953. Sec., Dr. W. J. German, 789 Howard Ave., New Haven 4, Conn.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written.* Various Centers, Feb. 6, 1953. Final date for filing applications is Nov. 1. Sec., Dr. R. L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Various Centers, January 1953. Final date for filing applications was July 1. *Practical.* Chicago, Oct. 6-10 and New York City, June 6-10, 1953. Sec., Dr. Edwin B. Dunphy, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: The deadline for the receipt of applications for the 1953 Part II examinations is Aug. 15. Sec., Dr. Harold A. Sofield, 122 S. Michigan Ave., Chicago.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Written.* Chicago, Oct. 6-10. *Oral.* Chicago, Oct. 6-10 and New Orleans, April 21-25, 1953. Sec., Dr. Dean M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Written and Oral.* Pathologic Anatomy and Clinical Pathology examination. Chicago, Oct. 9-11. Sec., Dr. William B. Wartman, 303 E. Chicago Ave., Chicago 11.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Chicago, Oct. 24-26; Boston, Dec. 5-7. Exec. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* New York, Sept. 26-28. Final date for filing of case reports is Aug. 15. Sec., Dr. Bradford Cannon, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE AND PUBLIC HEALTH: Cleveland, Oct. 18-20. Sec., Dr. E. L. Stebbins, 615 N. Wolfe St., Baltimore.

AMERICAN BOARD OF PROCTOLOGY: *Oral and Written.* Philadelphia, Sept. 27-28. Sec., Dr. Louis A. Buie, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York City, Dec. 15-16. Final date for filing applications is Sept. 15. Sec.-Treas., Dr. David A. Boyd, Jr., 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Oral.* Dec. 1-7. Final date for filing application was June 1. *Oral.* Tampa, April 8-15. Sec., Dr. B. R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various Centers. October 1952. Final date for filing application was July 1. *Written.* Various Centers, March 1953. Final date for filing application is Dec. 1. Sec., Dr. J. Stewart Rodman, 225 S. 15th St., Philadelphia.

AMERICAN BOARD OF UROLOGY: *Written.* Various Centers, December. *Oral.* Chicago, Feb. 7-11. Sec., Dr. Harry Culver, 30 Westwood Road, Minneapolis 16, Minn.

BOARD OF THORACIC SURGERY: *Written.* Various Centers, Sept. 5. Sec., Dr. William M. Tuttle, 1151 Taylor Ave, Detroit 2.

DEATHS

Gill, William Davis ✠ San Antonio, Texas; born in Dallas, Texas, Nov. 24, 1895; Vanderbilt University School of Medicine, Nashville, Tenn., 1917; specialist certified by the American Board of Ophthalmology and American Board of Otolaryngology; member of the Southern Medical Association, Texas Ophthalmological and Otolaryngological Society, American Academy of Ophthalmology and Otolaryngology, American Laryngological Association, American Laryngological, Rhinological and Otological Society, and the Association for Research in Ophthalmology; fellow of the American College of Surgeons; past chairman of the city board of health; served in the medical corps of the regular army from 1919 to 1927; awarded the French Medaille d'Honneur for services rendered during World War I; member of the staff, Nix Memorial Hospital, Medical Arts Hospital, and Santa Rosa Hospital, where he died May 24, aged 56, of chronic myocarditis.

Tedder, James William ✠ New Orleans; born in Magee, Miss., April 1, 1908; Tulane University of Louisiana School of Medicine, New Orleans, 1932; specialist certified by the American Board of Dermatology and Syphilology; member of the American Academy of Dermatology and Syphilology; formerly on the faculty of Louisiana University Medical Center; served during World War II, and was awarded the Bronze Star for heroic and meritorious service to survivors of a torpedoed, sunken ship in Langayen Gulf during the invasion of Luzon in the Philippines in January, 1945; on the staffs of Baptist and Charity hospitals and Touro Infirmary; died in Veterans Administration Hospital May 5, aged 44, of subdural hematoma and bronchopneumonia.

Garvin, Albert Henry ✠ Buffalo; born in Joliet, Ill., in 1881; Yale University School of Medicine, New Haven, 1903; an Associate Fellow of the American Medical Association; member of the American College of Chest Physicians, American Trudeau Society, and the American Clinical and Climatological Association; president of the Buffalo and Erie County Tuberculosis Association; consultant in tuberculosis at Millard Fillmore Hospital; at one time physician in charge of the New York State Hospital for the Treatment of Incipient Pulmonary Tuberculosis at Ray Brook, N. Y., and superintendent of the Spring Hills Sanatorium in Northville, Mich.; died May 28, aged 71, of cerebral hemorrhage.

Barrera, Severo Eugene ✠ Albany, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1929; served as professor of neurology and psychiatry at Albany Medical College and psychiatrist in chief and neurologist at Albany Hospital; formerly on the faculty of his alma mater, and principal research psychiatrist at the New York State Psychiatric Institute in New York; specialist certified by the American Board of Psychiatry and Neurology; member of the American Neurological Association, American Association of Neuropathologists, and the American Psychiatric Association; died in the Ellis Hospital, Schenectady, May 25, aged 51, of chronic cardiovascular disease.

Layman, Daniel Wunderlich ✠ Indianapolis; born in Putnamville, Ind., June 1, 1872; Columbia University College of Physicians and Surgeons, New York, 1898; clinical professor emeritus of otorhinolaryngology at Indiana University School of Medicine; specialist certified by the American Board of Otolaryngology; member of the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; served on the staffs of the Robert W. Long Hospital and James Whitcomb Riley Hospital for Children; died in Methodist Hospital April 21, aged 79, of arteriosclerotic heart disease and nephrosclerosis.

Allen, Lee Gilbert ✠ Litchfield, Ill.; Marion-Sims-Beaumont Medical College, St. Louis, 1902; past president of the Montgomery County Medical Society; on the staff of St. Francis Hospital; died June 10, aged 75, of coronary thrombosis.

Barrett, Edward William ✠ Medford, Mass.; Jefferson Medical College of Philadelphia, 1902; school physician; at one time city physician; on the staff of Lawrence Memorial Hospital where he died May 17, aged 82, of arteriosclerotic heart disease and bronchopneumonia.

Barthmaier, Othmar Frank, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1906; formerly on the faculty of his alma mater; served during World War I; affiliated with Hahnemann Hospital and St. Luke's and Children's Hospital, where he died May 9, aged 67, of arteriosclerosis.

Bates, George ✠ Kingston, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1890; died in Cass City May 13, aged 91.

Baum, E. Eldon ✠ Oklahoma City, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1928; served on the staffs of the Mercy and Wesley hospitals; died May 16, aged 56, of cerebral and kidney infarcts and bilateral tumor of adrenals.

Beeler, Bruce Henry, Evansville, Ind.; University of Louisville (Ky.) School of Medicine, 1915; served during World War I; affiliated with Deaconess Hospital and St. Mary's Hospital, where he died May 23, aged 64, of cancer and cirrhosis of the liver.

Bellak, Asher-Seelig, Philadelphia; Medico-Chirurgical College of Philadelphia, 1908; formerly affiliated with St. Agnes Hospital and the Mount Sinai Hospital, where he died May 19, aged 66, of tuberculosis.

Berger, Max Milton ✠ Oakland, Calif.; Rush Medical College, Chicago, 1935; served during World War II; assistant chief of urology, Veterans Administration Hospital; died April 30, aged 44, of coronary thrombosis.

Carleton, Elmer Howard ✠ Hanover, N. H.; Dartmouth Medical School, Hanover, N. H., 1897; formerly on the faculty of his alma mater; member of the New England Otolaryngological Society; served on the staff of the Dartmouth Eye Institute; in 1939 received the honorary degree of doctor of science from Bowdoin College, Brunswick, Me.; past president of the Dartmouth Medical School Alumni Association; died June 1, aged 83.

Clarke, William Thomas ✠ Los Angeles; University of Toronto Faculty of Medicine, Toronto, Canada, 1899; L.R.C.P., L.R.C.S., Edinburgh, 1904, and L.F.P.S., Glasgow, 1904; served during World War I; an Associate Fellow of the American Medical Association; died in California Lutheran Hospital May 11, aged 75, of cerebral thrombosis.

Collins, Elmer E. G. ✠ Chicago; Jenner Medical College, Chicago, 1910; formerly chief physician for Swift & Company, packers; died May 16, aged 68, of coronary thrombosis.

Coltharp, Ralph Weldon, Dallas, Texas; University of Texas School of Medicine, Galveston, 1942; specialist certified by the American Board of Psychiatry and Neurology; lieutenant in the U. S. Navy from 1942 to 1947; formerly director of the Boys Industrial School in Topeka, Kan.; consulting psychiatrist for the city school system; director of the Child Guidance Clinic; died May 25, aged 35, of septicemia.

Connell, John ✠ Jersey City, N. J.; New York Homeopathic Medical College and Hospital in New York, 1889; died in the Medical Center April 1, aged 87, of bronchopneumonia.

Cooper, Jacques ✠ Chicago; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1917; affiliated with Holy Cross Hospital; died May 9, aged 62, of heart disease.

Cress, Peter Joseph ✠ Marysville, Calif.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1908; died in Garmisch, Germany, May 30, aged 70, of coronary occlusion.

Cummings, Joseph Leo ✠ Poughkeepsie, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1934; specialist certified by the American Board of Psychiatry and Neurology; served during World War II; formerly member of

✠ Indicates Member of the American Medical Association.

the city board of health; neuropsychiatrist consultant, Veterans Administration Hospital in Castle Point; affiliated with St. Francis and Vassar Brothers hospitals; died May 28, aged 45, of metastatic carcinoma of the liver.

Duckworth, William Henry ✠ St. Clair, Mo.; National University of Arts and Sciences Medical Department, St. Louis, 1918; died in the Jewish Hospital May 3, aged 58, of heart disease.

Eckhardt, Peter, Rock Island, Ill.; Rush Medical College, Chicago, 1896; died in St. Anthony's Hospital May 9, aged 92.

Epstein, William George ✠ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1910; formerly on the faculty of Loyola University School of Medicine; member of the senior surgical staff, St. Bernard's Hospital, where he died June 16, aged 65, of myocardial infarction.

Erskine, James Pendleton, Lake Worth, Fla.; Columbia University College of Physicians and Surgeons, New York, 1903; formerly practiced in New York, where he was affiliated with New York Hospital, New York Eye and Ear Infirmary, and the French Hospital; died in West Palm Beach, May 25, aged 78, of cancer.

Evans, Samuel Davidson ✠ Pittsburgh; University of Pittsburgh School of Medicine, 1925; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology; instructor in ophthalmology at his alma mater; affiliated with Eye and Ear Hospital; died in St. Joseph's Hospital June 1, aged 51, of pneumonia and ulcerative colitis.

Harris, Henry, New York; Fordham University School of Medicine, New York, 1917; died recently, aged 59, of coronary occlusion.

Hasking, Arthur Perry ✠ Jersey City, N. J.; Columbia University College of Physicians and Surgeons, New York, 1903; past president and secretary of the Hudson County Medical Society; member of the American Psychiatric Association; for many years county physician; affiliated with Medical Center of Jersey City; died in Monmouth Memorial Hospital in Long Branch, May 29, aged 72, of cerebral hemorrhage and hypertension.

Haworth, Dillon Benjamin, Kansas City, Mo.; Kansas City (Mo.) Medical College, 1901; served during World War I; died May 22, aged 80.

Hiller, Frank Brooks ✠ Pinckneyville, Ill.; St. Louis College of Physicians and Surgeons, 1910; owner of a hospital bearing his name; died in Veterans Administration Hospital in Marion, May 6, aged 71, of coronary thrombosis.

Hirst, Virginius Bitzer ✠ New York; University of Virginia Department of Medicine, Charlottesville, 1918; associate clinical professor of otorhinolaryngology at Post Graduate Medical School of the New York University-Bellevue Medical Center; served during World War I; fellow of the New York Academy of Medicine and American College of Surgeons; affiliated with New York Eye and Ear Infirmary; died May 9, aged 61.

Hoenes, Andrew John ✠ Salt Lake City, Utah; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1889; an Associate Fellow of the American Medical Association; died May 29, aged 91, of arteriosclerotic heart disease.

Hoenig, Edward J. ✠ New York; Cornell University Medical College, New York, 1910; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; consulting gynecologist, and for two terms president of the medical board, Jewish Memorial Hospital; died May 3, aged 70, of coronary thrombosis.

Holt, Charles Scott ✠ Fort Smith, Ark.; St. Louis University School of Medicine, 1906; fellow of the American College of Surgeons; affiliated with St. Edward's Hospital and Sparks Memorial Hospital, where he died June 7, aged 72, of carcinoma of the prostate.

Kidd, James William, Fort Wayne, Ind.; Baltimore University School of Medicine, 1897; died in the Methodist Hospital May 29, aged 78, of arteriosclerotic heart disease.

Kissel, Julius Peter ✠ Centralia, Ill.; St. Louis University School of Medicine, 1910; served during World War I; died June 3, aged 63, of cerebral hemorrhage.

Kopelowitz, Jonas Clarence ✠ Los Angeles; Washington University School of Medicine, St. Louis, 1913; specialist certified by the American Board of Internal Medicine; served during World War I; affiliated with Cedars of Lebanon Hospital; died May 4, aged 60, of hypertensive heart disease.

Kosciolek, Stephen Frank ✠ Lowell, Mass.; Boston University School of Medicine, 1934; drowned in Northwood Lake, N. H., April 30, aged 45.

Kroll, Louis Joseph ✠ Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1936; died in Johns Hopkins Hospital, recently, aged 39, of glomerulonephritis.

Laessle, Henry Adolph ✠ Philadelphia; Jefferson Medical College of Philadelphia, 1902; also a graduate in pharmacy; specialist certified by the American Board of Otolaryngology; assistant professor of otolaryngology at Graduate School of Medicine, University of Pennsylvania; member of the Philadelphia Laryngological Society; died May 13, aged 80, of coronary thrombosis.

Lamb, Gerald E., Farwell, Mich.; Detroit College of Medicine, 1899; for many years county coroner; president of the Farwell State Savings Bank; died in the Henry Ford Hospital, Detroit, May 28, aged 76.

Lange, Sidney, Cincinnati; Medical College of Ohio, Cincinnati, 1903; professor emeritus of radiology, University of Cincinnati College of Medicine; specialist certified by the American Board of Radiology; member and past president of the American Roentgen Ray Society; affiliated with Good Samaritan, St. Mary's, and Cincinnati General hospitals; died in Jewish Hospital May 9, aged 72, of cerebral hemorrhage following a fall.

Levine, Emanuel ✠ Elizabeth, N. J.; University of Vermont College of Medicine, Burlington, 1938; served during World War II; died May 8, aged 37, of injuries received in an automobile accident.

Lewis, Harry Samuel ✠ Washington, D. C.; George Washington University School of Medicine, Washington, D. C., 1910; fellow of the American College of Surgeons; died May 14, aged 72, of coronary thrombosis.

Lichtenwalner, Howard Adams ✠ Bloomsburg, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1921; served during World War I; on the staff of the Bloomsburg Hospital, where he died May 12, aged 57, of cerebral vascular encephalopathy.

Light, Ralph Allison, Chanute, Kan.; University Medical College of Kansas City, Mo., 1898; veteran of the Spanish-American War; formerly secretary of the state board of registration and examination; for many years county coroner; retired surgeon of the Santa Fe Railroad; formerly member of the city council and school board; died in Neosho Memorial Hospital, June 3, aged 80, of hypostatic pneumonia.

Loefflad, Paul Aloysius ✠ Upper Darby, Pa.; Georgetown University School of Medicine, Washington, D. C., 1925; physician for many years of Villanova (Pa.) College; on the staff of the Fitzgerald Mercy Hospital in Darby, and Misericordia Hospital in Philadelphia, where he died May 18, aged 51, of bleeding duodenal ulcer.

Long, Homer Garrison, Copley, Ohio; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1897; died May 20, aged 80.

Lorenzo, Frank Alexander ✠ Punxsutawney, Pa.; Columbia University College of Physicians and Surgeons, New York, 1904; fellow of the American College of Surgeons; consulting surgeon, Elk County General Hospital, Ridgway, and the Adrian Hospital; died May 30, aged 72.

Love, Travis Drennon, Mendenhall, Miss.; Birmingham Medical College, 1915; died May 25, aged 67.

Marston, Charles Benjamin, San Rafael, Calif.; Hahnemann Medical College of the Pacific, San Francisco, 1908; past president of the board of education; on the staff of the San Rafael General Hospital, where he died May 19, aged 79, of cerebral accident and Parkinson's disease.

Martin, George Henry, Chicago; Northwestern University Medical School, Chicago, 1905; died June 27, aged 69.

Martinek, Jaroslav ⊕ Phoenix, Ariz.; University of Illinois College of Medicine, Chicago, 1946; died in Los Angeles May 28, aged 34, of bilateral pneumothorax and bronchial asthma.

Metzger, Karl Fenton, Belmar, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1933; died in Fitkin Memorial Hospital, Neptune, April 28, aged 45.

Mitchell, Allie Long, East Aurora, N. Y.; University of Buffalo School of Medicine, 1898; died in a Buffalo nursing home May 30, aged 97, of coronary thrombosis.

Nachtigall, Hans W., Chicago; Chicago College of Medicine and Surgery, 1913; for many years on the staff of St. Joseph Hospital; died May 24, aged 65, of coronary thrombosis.

O'Connor, Donald Charles ⊕ Buffalo; University of Buffalo School of Medicine, 1922; superintendent of the Edward J. Meyer Memorial Hospital, where he died May 25, aged 56, of hypertensive cardiovascular disease.

O'Donnell, John Joseph ⊕ Erie, Pa.; College of Physicians and Surgeons, Baltimore, 1904; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; served during World War I; affiliated with Hamot and St. Vincent's hospitals; died May 29, aged 70, of carcinoma.

Owen, William Arthur, Columbus, Ohio; Ohio Medical University, Columbus, 1897; died April 15, aged 78, of coronary thrombosis.

Pettit, James Kenneth ⊕ Atlanta, Ga.; Atlanta Medical College, 1914; served in France and Scotland during World War I; affiliated with the Veterans Administration; formerly on the staffs of the Georgia State Hospital for Insane in Milledgeville, Letchworth Village in Thiells, and Mansfield State Training School in Mansfield Depot, Conn.; died in Veterans Administration Hospital, Augusta, May 22, aged 63, of carcinomatosis.

Pinson, Fred Edward, Vicksburg, Miss.; Meharry Medical College, Nashville, Tenn., 1915; died May 26, aged 63, of injuries received in an automobile accident.

Plamondon, James Dillon, Lake Grove, Ore.; Willamette University Medical Department, Salem, 1898; served during World War I; formerly assistant superintendent of the Eastern Oregon State Hospital in Pendleton and Oregon State Hospital in Salem; served on the medical examining board of the Veterans Administration in Portland; died in Veterans Administration Hospital, Vancouver, Wash., May 15, aged 76, of a cerebrovascular accident.

Porter, MacGuyer ⊕ Elnora, Ind.; Eclectic Medical Institute, Cincinnati, 1897; died May 12, aged 85, of angina pectoris.

Posner, Benjamin Herman, Boston; Middlesex College of Medicine and Surgery, Cambridge, Mass., 1935; served during World War II; died April 5, aged 43, of coronary disease.

Praglin, Daniel Frank, Monterey Park, Calif.; Tulane University of Louisiana School of Medicine, New Orleans, 1929; served during World War II; died May 15, aged 49, of coronary thrombosis.

Pugh, Thomas Bryan, Napoleonville, La.; Charity Hospital Medical College, New Orleans, 1875; for many years coroner and sheriff of Assumption Parish; died May 4, aged 99.

Reilly, Maurice John ⊕ Arthur, Ill.; Chicago Medical School, 1931; served during World War II; died May 21, aged 47, of a heart attack.

Renaud, Joseph Edward ⊕ Syracuse, N. Y.; Syracuse University College of Medicine, 1927; medical director of the Easy Washing Machine Corporation; member of the Industrial Medical Association; affiliated with St. Joseph's Hospital, where he died May 9, aged 48, of cerebral hemorrhage.

Richmond, Oscar Lee, Corbin, Ky.; Vanderbilt University School of Medicine, Nashville, 1917; died May 27, aged 58.

Roberts, Daniel Stillwell, West Point, Ky.; Kentucky School of Medicine, Louisville, 1905; local surgeon for the Illinois Central Railroad; died May 18, aged 80, of diabetes mellitus.

Roberts, William James, Logansport, Ind.; Georgia College of Eclectic Medicine and Surgery, Atlanta, 1895; died in St. Joseph Hospital March 14, aged 81, of coronary occlusion.

Scott, Walter Sidney ⊕ Denver; Columbian University Medical Department, Washington, D. C., 1896; died March 6, aged 78.

Seitz, George William, Buffalo; University of Buffalo School of Medicine, 1902; died May 6, aged 77.

Shay, Francis Leo ⊕ New Haven, Conn.; Tufts College Medical School, Boston, 1925; member of the American Academy of General Practice; affiliated with Grace Unit, Grace-New Haven Community Hospital and Hospital of St. Raphael, where he died April 24, aged 53, of coronary thrombosis and virus pneumonia.

Sheridan, Joseph Morton, Baton Rouge, La.; Fordham University School of Medicine, New York, 1910; served during World War I; formerly affiliated with the New York City Farm Colony, West New Brighton, Staten Island, N. Y., New York City Cancer Institute Hospital, Welfare Island, New York, Morrisania and Gouverneur hospitals in New York; died May 4, aged 64.

Starzynski, Theophilus A., Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1904; served during World War I; died June 9, aged 73.

Stevenson, Benjamin J. ⊕ Sparta, Ill.; Homeopathic Medical College of Missouri, St. Louis, 1898; died March 8, aged 78, of carcinoma of the prostate.

Stuart, Clyde George ⊕ Los Angeles; College of Medical Evangelists, Loma Linda and Los Angeles, 1938; certified by the National Board of Medical Examiners; public health physician with county health department for many years; affiliated with White Memorial Hospital; died May 8, aged 49, of hypertensive heart disease.

Summers, Charles Raymond ⊕ Oak Park, Ill.; University of Illinois College of Medicine, Chicago, 1929; affiliated with West Suburban Hospital; died in Veterans Administration Hospital, Hines, June 11, aged 55, of chronic glomerulonephritis with uremia.

Tillotson, Harry Trudeau, Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1886; died June 15, aged 89, of coronary insufficiency.

Tittle, Lloyd Clay ⊕ Dallas, Texas; Baylor University College of Medicine, Dallas, 1918; died May 6, aged 61, of surgical shock with acute hepatic insufficiency.

Vander Bogart, Harry Eugene ⊕ Goshen, Ind.; the Hahnemann Medical College and Hospital, Chicago, 1914; served during World War I; member of the board of directors of the Goshen Hospital; died May 23, aged 68, of carcinoma of the ascending colon.

Voorhis, Anna E. Harvey ⊕ Mount Vernon, N. Y.; Woman's Medical College of the New York Infirmary for Women and Children, New York, 1893; formerly practiced in Yonkers, where she was affiliated with St. John's Hospital; died June 9, aged 85, of hypertensive arteriosclerotic disease.

West, Edward W., North Little Rock, Ark.; University of West Tennessee College of Medicine and Surgery, Memphis, 1904; died in the Provident Hospital, Chicago, May 25, aged 76, of cerebral hemorrhage and essential hypertension.

Wiener, Jacob Jesse ⊕ New York; Columbia University College of Physicians and Surgeons, New York, 1916; member of the American Academy of Pediatrics; affiliated with Hospital for Joint Diseases; died in Miami Beach, Fla., May 26, aged 58, of carcinoma of the colon.

Winne, William Ray ⊕ North Syracuse, N. Y.; Syracuse University College of Medicine, 1917; served during World War I; formerly county coroner; affiliated with Crouse Irving Hospital in Syracuse; died May 28, aged 61, of coronary disease.

GOVERNMENT SERVICES

ARMY

Lieut. Hopkins Awarded Soldier's Medal.—First Lieut. William C. Hopkins of Chicago, medical officer with the 25th Infantry Division in Korea, has been awarded the Soldier's Medal for "unselfish heroism and dauntless courage." The citation reads in part as follows: "On March 7, 1952, a helicopter crashed while attempting to evacuate two wounded soldiers from a foggy, wind-swept hill position near Sohuiri, Korea. With utter disregard for his personal safety, Lieutenant Hopkins ran through a known mine field to the crashed helicopter and aided in righting the flaming aircraft, rescuing one of the wounded soldiers and attempting to free the other man still trapped in the wreckage. He persisted in his efforts until the heat became unbearable and he was forced to move away from the craft.

"The helicopter pilot dashed into the flaming wreckage and tried again to rescue the trapped man. Realizing that the gas tank would soon explode, Lieutenant Hopkins ran into the inferno and forced the pilot away from the craft, saving him from permanent disfigurement and possible death. Lieutenant Hopkins' unselfish heroism and dauntless courage are in keeping with the highest traditions of the United States Army."

Lieutenant Hopkins is the son of Percy E. Hopkins, M.D., of Chicago, a former president of the Illinois State Medical Society.

DEPARTMENT OF DEFENSE

Korean Society News.—Col. Walter M. Bartlett, Decatur, Ga., Medical Consultant at Eighth Army Headquarters, has been elected president of the "38th Parallel Medical Society of Korea," and Capt. Inger Schulstad, a woman doctor with the Norwegian Surgical Hospital, secretary. They succeed Lieut. Col. Charles E. Mason, Alhambra, Calif., I Corps surgeon, the outgoing president, and Capt. Ruth Dickson, Vinton, Va., chief nurse of the 8,055th Mobile Army Surgical Hospital, former secretary.

The new vice-presidents are Col. Erling F. Hjort, commanding officer of the Norwegian Surgical Hospital; Col. Morgan Smith, Canada, newly-appointed surgeon of the First Commonwealth Division; Capt. Louis Kirkpatrick, USN, Reagan, Texas, First Marine Division Surgeon; Lieut. Col. Claude B. Knight, Wewoka, Okla., 45th Division Surgeon; Lieut. Col. Sin Jai Kuh, commanding officer of the 5th Republic of Korea Mobile Army Surgical Hospital; Lieut. Col. A. G. Rangaraj, commanding officer of the 60th Indian Field Ambulance Unit, and Lieut. Col. H. Haskell Zipperman, Mount Holly, N. J., commanding officer of the 8,063d Mobile Army Surgical Hospital. This unique society, which is composed of medical personnel in I Corps and adjacent IX Corps areas, meets twice a month on the 38th parallel. Speakers at the most recent meeting were Colonel Hjort of the Norwegian Hospital and Capt. Edward Jahnke, Pittsburgh, Pa., from Walter Reed Army Hospital, Washington, D. C.

VETERANS ADMINISTRATION

New GI Bill for Veterans.—The President has signed a new GI Bill for veterans who served in the armed forces any place in the world since the start of the Korean conflict on June 27, 1950. The new law provides five benefits, all designed to assist veterans in their return to civilian life. The benefits include education and training; guaranteed or insured loans for homes, farms, and businesses; unemployment compensation; mustering-out pay; and job finding help.

The education and training provisions allow a veteran one and one-half days of training for each day in service after the outbreak of the Korean fighting, regardless of where the service was performed, up to a maximum of 36 months; however, veterans who have previously trained under earlier veterans' training laws, the World War II GI Bill or Public Laws 16 or 894 for the disabled, may get up to 48 months, minus whatever time they have already spent in training under those earlier programs. A veteran may train in school or college, on the job or on the farm, as long as the school or training establishment has been approved by an appropriate state approving agency and meets other qualifications of the law.

Veterans in GI Bill training will receive an education and training allowance each month from the government to meet part of the expenses of their training and living costs. Tuition, fees, books, supplies, and equipment will not be paid by the government; instead, they will be paid out of the monthly allowance. Rates for veterans in full-time training in schools and colleges are $110 a month if they have no dependents, $135 if they have one dependent, and $160 if they have more than one dependent. Those in training less than full time will receive lower monthly rates. Top monthly amounts for on-the-job trainees are $70 without dependents, $85 with one dependent, and $105 with more than one dependent. The maximal allowances for institutional on-farm trainees are $95, $110, and $130, respectively. The law requires that on-job and on-farm rates be reduced, at four month intervals, as the training progresses and the veteran's own earnings increase. Veterans were reminded that the last three benefits of the new GI Bill, unemployment compensation, mustering-out pay, and job-hunting aid, are not administered by the Veterans Administration. Veterans should not write to the VA about them if they want further information or have questions to be answered; instead, they should correspond directly with the agency concerned. Education and training, for post-Korea veterans, must be started by Aug. 20, 1954, or two years after release from active duty, whichever comes later. No training may be given beyond either seven years after discharge or seven years after the end of the current emergency, whichever is later.

MISCELLANEOUS

Science Foundation to Compile Research Information.—Federal agencies supporting scientific research and development programs have been asked to supply the National Science Foundation with statistical and fiscal information about their programs for the fiscal years 1951 and 1952. The foundation is compiling such information at the request of the Bureau of the Budget, which has gathered similar information in previous years. The final report, which it is hoped will be available before Jan. 1, 1953, will be of value also to Congress and to the agencies, themselves, in the administration and planning of their programs. The information will be of value to the foundation, also, in fulfilling its statutory responsibilities with respect to scientific research and its studies concerning the effect of present support and policies on research and education in the institutions of the country.

The information will be compiled under various functional classifications, including basic research, applied research, development, and increase of research and development plant, and subject classifications including biologic, medical, agricultural, physical, mathematical, engineering, and social sciences. Typical examples of nonprofit institutions for which information will be gathered are colleges and universities, research institutes, research foundations, experiment stations, hospitals, libraries, museums, observatories, and corporations organized specifically to do scientific research and development for the federal government on a nonprofit basis. Information on direct research activities of agencies of the federal government will be excluded, but the report will include information on federal support to agencies of state, local, or foreign governments.

FOREIGN LETTERS

BRAZIL

Colon Resection with Immediate Open Anastomosis.—Dr. E. da Silva Bastos, professor of surgery at the São Paulo State University, recently reported a series of 72 patients on whom he performed resection of the colon followed by immediate open anastomosis. Except for four of the cases, two with tuberculomas of the cecum and two with inflammatory strictures from diverticulitis, all were due to cancer of the colon, the cecum, and the rectum. In the 72 cases, 12 with Mikulicz resection, 23 with closed anastomoses, and 37 with open anastomoses, there were four deaths (5.53%), one from generalized peritonitis after an ileocolic closed anastomosis, one from hypoproteinemia as a consequence of a hematoma, one from uremia, and one from cerebral thrombosis. In the cases in which closed anastomosis was performed there was one death (4.35%), and in the cases with open anastomosis there was also one death (2.70%). There were 5 complications in 12 cases of resection by the Mikulicz technique, the most frequent of which were abscesses of the intestinal wall and eventrations. In only one case of eventration was there no accompanying subcutaneous abscess. In the group of closed anastomoses, the most frequent complication was stricture, which occurred in five cases and probably also in two cases of dehiscence of the suture with abscess or fecal fistula. Closed anastomosis, used in two cases of resection of the rectum, caused stricture with fecal fistula in both. In one of the cases, the fistula was very wide, remaining so until the death of the patient 18 months after the operation. Open anastomosis, used in 16 cases without colostomy, caused fewer complications. There were four cases of fecal fistula, all of them in previous resections of the rectum. All fistulas were of little importance, disappearing spontaneously within a short time. Only one fistula occurred in a patient without colostomy; in the other three patients a minimal colostomy had been done. The author concludes that the open anastomosis is superior to the closed anastomosis for the following reasons. 1. It is a simpler technique, not needing special instruments. 2. The suture is easier; the stitches are made directly through the walls of the intestine under direct vision. 3. The suture is tighter and the approximation of the intestinal layers more perfect.

Hemagglutination with Human Red Blood Cells and BCG Tuberculin.—Dr. Laerte de Andrade, of the Oswaldo Cruz Institute, and Dr. Candido Silva, of the division of leprosy, National Department of Health, have just reported the results of their extensive investigations on the hemagglutination test of Middlebrook and Dubos and its use in connection with tuberculosis and leprosy. In the introduction of their report the authors state that, owing to the difficulty of obtaining in Brazil specific antigens prepared with the polysaccharide fraction of the tubercle bacillus or the Lederle tuberculin (O.T.) recommended by American investigators, they tried to use several tuberculin preparations made in the country. The only one that gave good results was prepared by cultivation of BCG on a Sauton medium. The authors performed 271 tests on serums from blood donors as well as from tuberculous and leprous patients. Human O Rh-negative red blood cells sensitized by BCG tuberculin were used for the test. A qualitative test very useful for routine work was performed in capillary tubes, as an adaptation of Chown's test for Rh antibodies.

The 271 serums examined included 68 from tuberculous patients, 116 from leprous patients, and 87 from donors from the blood bank of the Rio de Janeiro Hospital dos Servidores. There were 16 negative serums (23.5%) among the tuberculous patients, 22 (18.9%) among the leprous patients, and 82 (94.3%) among healthy blood donors. Of the 52 tuberculous patients with positive results, 19 showed results with titers of 1:32 or less and 33 showed results with titers from 1:64 to 1:1024. Of the 94 leprous patients with positive results, 40 showed results with titers 1:32 or less and 54 showed results with titers 1:64 to 1:1024. Of the 87 blood donors, only 5 showed positive results (3 with a titer of 1:4, one with a titer of 1:8, and one with a titer of 1:16). The 116 leprous patients included 11 of the undetermined form, 15 of the tuberculoid form, and 86 of the lepromatous form. Of the latter, 43 patients had active leprosy and 43 were in clinical regression, without bacilli in the nasal mucus and in the skin, and were scheduled to be transferred to the outpatient department. Among the patients with the lepromatous form in clinical regression, 14 showed negative results of the hemagglutination tests, and many of the others had very low positive agglutination titers. Three of them, however, had very high titers (1:256 and 1:1024). The authors explain these results as being caused by visceral leprosy, which probably did not show a regression similar to that of the tegumentary forms. In this connection, the authors' conclusion is that the Middlebrook-Dubos test is useful in supplying some indispensable information as to the course of the disease in patients with the lepromatous form and especially of candidates for transferral to the outpatient department.

Milestone in Campaign Against Yellow Fever.—A milestone has been reached in 1951 in the campaign against yellow fever in Brazil: the complete eradication of Aedes aegypti, the urban vector of the disease. A recheck is being made, however, in some parts of the eastern and northeastern regions, where the environmental conditions are very favorable to that species of mosquito, although the work done during the first five months of the current year in those areas has supposedly eradicated the mosquito. There still must be careful and continuous inspections in order to prevent the reimportation of the mosquito through the borders, and air and maritime ports, since A. aegypti still exists in 23 countries and possessions and colonies in the Americas.

The sylvan form of yellow fever is transmitted through other species of mosquitos. The last three cases of urban yellow fever were reported in 1937, and after this only the sylvan form of the disease was recorded in Brazil. During the three 5 year periods 1937-1941, 1942-1946, and 1947-1951 there were, respectively, 807, 141, and 45 cases of the disease. The campaign against the sylvan form of yellow fever includes mainly vaccination, viscerotomy, and laboratory examinations. About 900,000 persons were immunized against yellow fever in 1951, bringing the total number of vaccinations, since 1937, to more than 7 million. Immunization is mainly used to protect persons who have to work or live in forests. Viscerotomy is the best resource for the discovery of the silent foci of the disease in areas in which it frequently goes unrecognized even by trained physicians. There were, in 1951, a total of 1,324 localities with viscerotomy service, which sent 8,185 specimens of liver to be examined in the laboratory.

DENMARK

Civil Defense and Biologic Warfare.—In 1951 the governing body of civil defense requested the Danish public health authorities to compose a memorandum on civil defense problems connected with biologic warfare. In December of that year, the public health authorities appointed a committee of bacteriological, epidemiological, clinical, and administrative experts to pre-

The items in these letters are contributed by regular correspondents in the various foreign countries.

pare such a memorandum. The completed memorandum is concerned with successfully combating the results of biologic warfare. The sources of information that the committee used are official publications and are available to all persons interested. The memorandum refers, of course, particularly to conditions that exist or may develop in Denmark. The authors conclude that biologic warfare is possible in theory and feasible in practice, although its effects cannot be calculated with certainty. They also conclude that though biologic weapons can be directed against military objectives, their employment undoubtedly greatly endangers civilians. Panic among civilians may be the only effect sought by an aggressor anxious to demonstrate his strength and to threaten the government of an enemy country. The possibilities for sabotage with biologic weapons are almost unlimited, and the fifth columnist can do his work with greater accuracy and with fewer weapons than a regular combatant. Many germs can be cultivated in great quantities under primitive conditions in secrecy in the country to be attacked. In Denmark an attack with infected insects is not likely to be successful owing to its climate and its indigenous insects, but yellow fever and rickettsia may be conveyed not only by insects but also by inhalation. The weight and volume of biologic weapons are so small that it may be impossible to prevent their entry into a country by smuggling. For this and various other reasons, attention must be focused on preventing the effects once such warfare has started. In Denmark there are not enough vaccines for vaccinating all persons in a community against all the diseases spread in biologic warfare, but it should be possible to produce a botulinus vaccine suitable for limited and much exposed sections of the community. The prophylactic employment of antibiotics presupposes enormous quantities of them, and they would have to be limited to sections of the community greatly exposed to infection. Penicillin and the sulfonamides are now produced in Denmark in sufficient quantities for an emergency of limited duration, but the cost of well-known antibiotics produced abroad is prohibitive.

Protests Against Wholesale Legal Abortions.—The Hippocratic attitude towards the induction of abortion has lately been defended by Prof. Erik Rydberg, in whose hospital abortions are induced only on strict and clear medical indications. Writing in the organ of the Danish Medical Association, *Ugeskrift for Laeger*, for May 22, he reports that the number of legally induced abortions has risen considerably since the adoption of the abortion law in 1937 and its practical application after 1939. Between 1940 and 1950 the number of legal abortions has risen from 522 to 3,969. It is calculated that in Copenhagen in 1951 the legal abortions were equivalent to 12% of all the confinements in this year. The annual reports of gynecologic hospitals suggest that most legal abortions are indicated by psychiatric considerations. For example, at the gynecologic department of the Frederiksberg Hospital in 1950 the 319 legal abortions included 267 induced on psychiatric grounds.

Declining Tuberculosis Rate in Childhood.—Several articles in the medical press have lately asked the reason for the tuberculosis morbidity declining more rapidly at the school age than at the preschool and postschool ages. They also wondered whether BCG vaccination offers any answer to this question. Dr. E. Groth-Petersen, who is in charge of the tuberculosis dispensary work of the County of Praestö, has studied the characteristics of tuberculosis in his district since a tuberculosis dispensary was started there in 1943. Between then and 1951 there was no great decline in the tuberculosis morbidity at the preschool age, at which BCG vaccination is comparatively rare. On the other hand, at the school age, from 7 to 14 years, the tuberculosis morbidity showed an abrupt fall, which has been maintained since 1947. Between the ages of 15 and 19 there was a more gradual fall. Practically every schoolchild found to be tuberculin-negative was vaccinated with BCG after 1943. After discussing the possibilities that the decline of the tuberculosis morbidity might be due to less exposure to infection or to changes in diagnostic standards or to other factors, Dr. Groth-Petersen concludes that the abrupt fall in the tuberculosis morbidity between the ages of 7 and 14 years can largely be explained as the outcome of wholesale BCG vaccination in school.

In another study, Dr. Jörgen Kringelbach compared the tuberculosis clientele of a children's hospital in the two years 1940 and 1950. This hospital, the only one of its kind in Denmark, dealt with tuberculous children from Copenhagen. Its 47 beds were, for many years, always in use for tuberculous patients, but of late most of them have been allocated to nontuberculous patients for want of enough tuberculous children. In the two years under review there was little difference in the number of preschool children, whereas there was a marked drop in the number of children of the school age, 7-14 years. The relative scarcity of the school age patients in 1950 is held by Kringelbach to be largely due to the extensive BCG vaccination of Copenhagen's tuberculin-negative school children in 1948 and 1949. There was a marked difference between the two years 1940 and 1950 with regard to the duration of hospitalization, which was 100 days on the average in 1940 as compared with only 62 days in 1950. The character of the disease was on the whole less serious in 1950 than in 1940 to judge by the radiological findings, the temperature, and the erythrocyte sedimentation rate. Thus in the brief span of 10 years a profound change had come over the clientele of this hospital.

PARIS

Iodochlorhydroxyquin in Experimental Tuberculosis.—P. E. David and F. Tisson reported to the National Academy of Medicine the first in vivo trials against tuberculosis of an iodochlorhydroxyquin suspension. Two groups, of 10 animals each, were inoculated with a human virulent strain of tuberculosis. At the end of three weeks one group was treated by daily subcutaneous administration of 3 cg. per kilogram of body weight of the drug while the other served as untreated controls. Eight weeks after the inoculation one guinea pig was killed in each group, the others being killed at intervals within the following 15 days. The results of the autopsy of these animals revealed that of the 10 animals who were given iodochlorhydroxyquin, 7 showed only lymph node involvement of the ganglions (stage 1), 1 an involvement of lymph nodes and spleen (stage 2), and 2 an involvement of lymph nodes, spleen, and liver (stage 3); none of these animals reached stage 4 (lymph nodes, spleen, liver, and lungs involved). On the other hand, of the 10 untreated control animals, 5 were in the disease stage 4, 1 in stage 3, and 4 in stage 2. None of the control animals remained in stage 1. Swabs of inguinal abscesses showed the presence of a larger number of bacilli in all control animals than in the treated group.

Microbial Substitution and Selection in Chronic Infections.—The failure of some therapy with antibiotics has been explained by the resistance acquired by bacteria in the course of treatment. It has also been found, in other cases, that the organism sets off a mechanism of the adaptation enzymes; for instance, penicillinase undergoes a morphological change, taking either the dwarf or the L form, according to Tulsane. J. Brissou of the French navy, on the basis of clinical and laboratory observations, noted that after a patient is treated with an antibiotic a relapse may occur after a transient improvement and the disease may become chronic. A further examination reveals new bacterial flora. There is a substitution of bacteria, and it is noted that, in this selection, resistant species are present. The author noted the substitution in urine of proteins or Klebsiella by Escherichia coli, of Proteus by enterococci and, in urethritis, the substitution of streptococci by gonococci. In an unpublished work done in collaboration with Ardisson, the author shows that, after massive doses of an antibiotic, the rich intestinal flora decreases and there is an upset of the bacterial equilibrium accompanied by new disorders, notwithstanding the elimination of Salmonella or Shigella. The author suggests a new idea of the cause of chronic diseases by selection and substitution of bacteria.

CORRESPONDENCE

PATIENTS WITH POLIOMYELITIS

To the Editor:—I have read with interest the article entitled "Home Care of Patients with Acute Poliomyelitis" by Philip M. Stimson, M.D., published in THE JOURNAL (June 21, 1952, page 719). There is no question but that the emotional attitudes of the family and patient are important. Hospitalization in many instances is unnecessary, and long periods of transportation are detrimental; however, I do feel it necessary to comment on some other considerations.

In the recognizable case without paralysis, it is well known that the severity of the early signs and symptoms bears no direct relationship to prognosis in regard to either life or developing weakness. Also, changes in the patient's condition can develop rapidly, and, if the patient is hospitalized, appropriate measures can be immediately instituted. However, if the patient is at home, the attendant may not notice the signs, the physician may not be located promptly, and the transportation to the hospital occur at a most inappropriate time from the point of view of the patient's welfare.

In some areas private duty nurses are scarce, and, if the patient remains at home, his care will be the responsibility of nonmedical attendants. If a diagnosis is made late in the disease, when the temperature is returning to normal and care is adequate, home care has advantages. However, we are preaching early diagnosis, and it would seem that the lack of relationship between early signs and symptoms and prognosis would indicate that hospitalization in early cases is preferable.

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EOSINOPENIC RESPONSE TO EPINEPHRINE

To the Editor:—It is unfortunate that so many investigators, such as Drs. Charles W. Dowden and James T. Bradbury (Eosinophil Response to Epinephrine and Corticotropin: Studies in Alcoholics and Nonalcoholics, *J. A. M. A.* **149**:725-728 [June 21] 1952) continue to use subnormal eosinopenic response to injection of epinephrine as a means of testing pituitary-adrenal function.

In 1950, on the basis of animal investigations, Thorn and his associates (Recant, Hume, Forsham, and Thorn: Studies on the Effect of Epinephrine on the Pituitary-Adrenocortical System, *J. Clin. Endocrinol.* **10**:187, 1950) postulated that the hypothalamus, pituitary, and adrenal cortex are successively stimulated to produce epinephrine eosinopenia. Thorn and Forsham wrote that ". . . a fall of 50% or more in circulating eosinophils (after injection of epinephrine) excludes the presence of serious pituitary A.C.T.H. or adrenal cortical insufficiency," (Thorn and Forsham: Clinical Tests for Adrenal Cortical Reserve, in Progress in Clinical Endocrinology, Soskin, S., editor, New York, Grune and Stratton, 1950, p. 213). However, a large number of physicians interpret the test erroneously. They believe that an inadequate response, i. e., of less than 50% fall, indicates disease or relative dysfunction of the hypothalamus, pituitary, or adrenal cortex.

My colleagues and I have observed greater than 50% drop of eosinophils following injection of epinephrine in patients with pituitary tumors and in patients who were subjected to adrenalectomy and who were receiving small doses of cortisone. Responses of less than 50% were seen in a large number of patients with unrelated pathological conditions (Best, Muehreke, and Kark: Studies on Adrenocortical Eosinopenia, abstract, *J. Clin. Investigation* **30**:629, 1951; Best, Muehreke, and Kark: Clinical and Statistical Evaluation of Four-Hour Eosinophil Response Tests, abstract, *J. Lab. & Clin. Med.* **38**:790, 1951; Muehreke and others: Mechanisms of Adrenocortical Eosinopenia: Antagonisms Between Heparin and Cortical Hormones and the Action of Epinephrine Post-Adrenalectomy, *Proc. Inst. Med. Chicago* **19**:68, 1952. Kark and Muehreke: Does Adrenaline Eosinopenia Reflect Pituitary Adrenal Function in Man? *Lancet* **1**:1189-1191, 1952. Best, Muehreke, and Kark: Studies on Adrenocortical Eosinopenia: A Clinical and Statistical Evaluation of Four-Hour Eosinophil Response Tests. *J. Clin. Investigation*, to be published). These observations, together with clinical and statistical analysis of 702 four-hour response tests in 284 persons, indicate that the epinephrine test is of little value in the diagnosis of adrenal, hypothalamic, or pituitary disease; nor does it accurately assess the function of these three organs.

The verbal reports given two weeks ago at the annual meeting of the Endocrine Society indicate that injection of epinephrine into healthy persons does not produce a uniformly significant increase in urinary 17-ketosteroid excretion (Jeffries and Bochner: A Comparison of Effects of Single Injection of A.C.T.H. and Epinephrine upon Adrenal Cortical Activity) or in blood levels of 17-hydroxycortico-steroids (Nelson, Sandberg, Palmer, and Glenn: Levels of 17-Hydroxy-Corticosteroids Following Intravenous Infusion of Epinephrine into Normal Men). Our observations and these two reports indicate that the mechanisms of epinephrine-induced eosinopenia are yet obscure. Therefore, we believe the epinephrine response test should be abandoned in clinical practice, at least until the mode of action is clarified. Moreover, the test should not be used to test pituitary-adrenal activity in groups of patients. Proper assessment of functional endocrine changes in alcoholics, in schizophrenics, and in others must await assay of corticotropin and adrenal steroids in these patients.

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POSTPARTUM HEMORRHAGE

To the Editor:—In THE JOURNAL of June 21, 1952, there is an article by Dr. Ernest Myller titled "Control of Postpartum Hemorrhage" (page 757). In this article I am quoted as saying it is my "belief . . . that when the first uterine packing is not successful, the uterus is probably ruptured. If such is the case, a second packing is definitely contraindicated." This is not only a complete misquote, it is also contrary to my teaching of a number of years.

The correct quotation from the source used by Dr. Myller is ". . . severe postpartum hemorrhage which does not respond to massage and the rather efficient oxytocic agents, when given intravenously, particularly when it occurs in the multigravida, is quite likely to be due to a partial or a complete rupture of the uterus. If this be present, packing will not only do no good, but will actually be harmful, in that vitally necessary time will be lost."

Actually, in our clinics at the University Hospital, Baltimore, and the Baltimore City Hospitals, the uterine pack has not been used to control postpartum hemorrhage for more than six years, representing about 30,000 consecutive deliveries. It is my belief that the uterine pack to control postpartum hemorrhage has absolutely no place in present-day obstetrics.

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FUNGUS INFECTIONS

To the Editor:—In the editorial "Fungus Infections Complicating Antibiotic Therapy," which appeared in THE JOURNAL, June 21, 1952, page 762, mention is made that my co-workers and I reported six instances of pulmonary moniliasis. This notation is inserted in a paragraph in such a way that it would appear that these six instances followed the use of one of the antibiotics discussed in the article. I would like to correct this impression and note that all the patients studied had pulmonary moniliasis and received no antibiotic therapy and that each of these patients was studied in the era before aureomycin, chloramphenicol, and terramycin came into general use.

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BUREAU OF LEGAL MEDICINE AND LEGISLATION

MEDICOLEGAL ABSTRACTS

Malpractice: Drainage Tube Left in Patient Following Operation.—The plaintiff sued for damages alleged to have been caused by the malpractice of the defendant physician. The jury found in favor of the plaintiff, but the trial judge entered judgment for the defendant notwithstanding the verdict. The plaintiff therefore appealed to the Supreme Court of California.

The plaintiff consulted the defendant physician concerning a severe pain in his scrotum. The ailment was diagnosed as a varicocele, and an operation was recommended and performed by the defendant. The plaintiff told the defendant that he did not want to lose his left testicle, and the defendant said that the operation was a simple one and that if the testicle was healthy there would be no occasion for its removal. Shortly after the operation the defendant told the plaintiff's mother that the left testicle was smaller than the other one but that it appeared healthy and he had not removed it. The day following the operation the plaintiff's scrotum began to swell and become painful. The dressings had to be removed. The evidence showed that at that time the operative incision was tightly sewed and that no drainage tube protruded from it. Penicillin was administered, but the swelling continued, and about a week after the operation the defendant probed the wound with surgical forceps to establish drainage and directed the plaintiff to take sitz baths. After about two weeks he was taken home but was instructed to continue the baths and to walk as much as possible. His mother helped him with the baths and dressed the incision. About two months after the operation, while cleaning pus from the probe wound, the plaintiff and his mother noticed, deep in the wound, the edge of a substance that resembled "a muscle." When this substance was touched with the swab stick, about an inch of white rubber tube protruded. On the following morning, the rubber tube stuck to a dressing and came out. The plaintiff and his mother described it as being "very wet and full of pus." This was the first time either the plaintiff or his mother knew that a rubber tube had been inserted in his scrotum. The plaintiff immediately telephoned the defendant who said: "That is fine. I left it for a drain. I am glad you found it." The defendant then advised the plaintiff that a further operation would be necessary and that the left testicle would have to be removed. This operation was performed by the defendant assisted by Dr. Gummess, who had also assisted at the first operation. The left testicle was removed, and a drainage tube was inserted, its presence being indicated on the operative report. Several days later the drain was removed, and the plaintiff left the hospital. It was the plaintiff's contention that a rubber drainage tube had been negligently left in the incision after the first operation and that such negligence resulted in the necessity for the removal of his left testicle.

Concerning the first operation, the defendant testified that he had placed a rubber tube in the plaintiff's scrotum for drainage purposes. He described it as being attached to the wall of the scrotum by sutures, part of the tube protruding from a "stab wound" made in the lowest part of the scrotum. He admitted, however, that he told no one except Dr. Gummess of the tube. He did not tell the interns or nurses of its presence and "overlooked" mention of the tube or stab wound in making his operative report, although it called for pertinent information on drainage. When asked whether the tube might have slipped entirely inside the scrotum, the defendant replied that such was ". . . within the realm of possibility . . . ." Dr. Gummess substantiated the defendant's testimony as to the insertion of the tube but said that he did not see it at any time when he examined the patient after the operation. As a practicing specialist in urology, Dr. Gummess was asked whether ". . . in an operation for the removal of a varicocele, under proper medical and surgical practice here, would a physician and surgeon intentionally permit a wound to close, leaving a rubber tube within the scrotum, with no part of the rubber tube protruding?" He replied, "No, he would not." It was further established, by expert testimony, that drainage of scrotal wounds is a mandatory rule because "proper drainage will prevent infection." Two experts identified the pain and other symptoms of disease in the plaintiff's scrotum after the operation as "classical signs" and "indications" of infection, which indicates bacterial attack on living tissue. The defendant admitted that there was infection present in the incision that was draining and that the draining involved the testicle, the spermatic cord, and the scrotum. Such infection, he said, can cause tissue to become necrotic.

On this evidence the jury returned a verdict in favor of the plaintiff, but as previously stated, the defendant's motion for judgment notwithstanding the verdict was granted. A defendant's motion for judgment notwithstanding the verdict, said the supreme court, may properly be granted only when, disregarding conflicting evidence and indulging in every legitimate inference that may be drawn from the plaintiff's evidence, the result is a determination that there is no evidence sufficiently substantial to support the verdict. Relying on this rule, the plaintiff contended that the evidence, disregarding conflicts, and the legitimate inferences to be drawn from it furnished sufficient support for the jury's implied finding that the defendant was negligent in performing the varicocelectomy, which negligence proximately caused the subsequent removal of the testicle.

The record fully supports the plaintiff in this regard, said the Supreme Court. From the evidence presented by the respective parties, the jurors reasonably might have concluded that the rubber tube was completely enclosed within the scrotum at the time of the operation and the incision tightly sutured. If, however, they chose to believe that the defendant left the tube protruding, there is ample evidence tending to prove a failure to fasten it so as to prevent withdrawal into the scrotum, a possibility admitted by the defendant. On either view of the evidence, it shows a surgical procedure that permitted the operative incision to become tightly closed, leaving the rubber tube completely within the scrotum. One of the physician witnesses in the case testified that "It is a rule, it is a mandatory rule, that we always drain scrotal wounds . . . ." The evidence would justify a conclusion that the defendant violated this "mandatory rule" by failing to drain the scrotum during the period following surgery, either because he made no provision for drainage or because he permitted the drainage tube to slip into the scrotum and the operative incision to close completely.

There is no merit, the Supreme Court continued, in the contention that the evidence failed to establish a causal relation between the failure to properly provide for drainage and the subsequent necessity for removal of the testicle. "The law does not require that negligence of the defendant must be the sole cause of the injury complained of in order to entitle the plaintiff to damages therefor. All that is required . . . is that the negligence in question shall be *a* proximate cause of the injury . . . ." It was shown that at the time of the first operation the plaintiff's testicle was healthy and for that reason the defendant did not remove it. Yet, 42 days later, it was in such condition that removal was deemed necessary. Although the defendant argued to the contrary, the jury's implied finding that a causal relationship existed was not purely speculative. According to the medical testimony, the reason for the "mandatory rule" of drainage is the danger of infection. That testimony also characterized the plaintiff's symptoms after the operation as "classical signs" and "indications" of infection, and unquestionably it was a necrotic condition that necessitated the second operation.

Accordingly, the Supreme Court reversed the judgment of the trial court in favor of the defendant physician with directions to the trial court to enter judgment in favor of the plaintiff. *Champion v. Bennetts, 236 P. (2d) 155 (California 1951).*

MEDICAL LITERATURE ABSTRACTS

UNITED STATES

A.M.A. Arch. Ophthalmology, Chicago

47:415-550 (April) 1952

Experiences with Tumors of Retina. K. C. Swan and S. Hyman.—p. 416.
Toxoplasma Chorioretinitis in Adults: Preliminary Study of 41 Cases Diagnosed by Microscopic Examination. H. C. Wilder.—p. 425.
Effectiveness of Terramycin and Other Antibiotics Against Experimental Bacterial Keratitis. E. J. Cannon and I. H. Leopold.—p. 426.
Sympathetic Ophthalmia: Similarity to Bilateral Endophthalmitis Phacoanaphylactica; New Therapeutic Methods. G. M. Haik, R. L. Waugh Jr. and W. Lyda.—p. 437.
Familial Glaucoma: Report of Pedigree. W. G. Frey and A. Posner. —p. 454.
Effect of Cortisone upon Corneal Vascularization Produced Experimentally. I. C. Michaelson.—p. 459.
Intraocular Rubber Foreign Bodies After Surgery. R. J. Brockhurst. —p. 465.
Subhyaloid Hemorrhage and Exophthalmos Due to Ruptured Intraventricular Aneurysm: Case Occurring in Toxemia of Pregnancy. T. Bisland and A. Topilow.—p. 470.
Studies in Experimental Ocular Tuberculosis: XVI. Effect of Corticotropin, Cortisone, and Compound F on Development of Experimental Ocular Tuberculosis in Immune-Allergic and Normal Rabbit. A. C. Woods and R. M. Wood.—p. 477.

A.M.A. Arch. Surgery, Chicago

64:409-534 (April) 1952

*Cardiac Arrest. L. C. Reid, H. E. Stephenson Jr. and J. W. Hinton. —p. 409.
Major Surgery in Old People. C. A. Haug and W. A. Dale.—p. 421.
Pilonidal Sinus: Evaluation of Plastic Closure Using Flaps of Gluteal Muscle. R. W. Dwight.—p. 438.
Fractures of Shaft of Tibia and Fibula: Comparative End-Results from Various Types of Treatment in Teaching Hospital. E. B. Carpenter, J. J. Dobbie and C. F. Siewers.—p. 443.
Anterior Herniation of Ruptured Lumbar Intervertebral Disk: Comments on Diagnostic Value of Diskogram. R. B. Cloward.—p. 457.
Effects upon Lung of Varying Periods of Temporary Occlusion of Pulmonary Artery. H. A. Davis, W. B. Gordon, E. W. Hayes Jr. and M. T. Wasley.—p. 464.
Stenosing Tenovaginitis at Wrist and Fingers: Report of 423 Cases in 369 Patients with 354 Operations. P. W. Lapidus and R. Fenton. —p. 475.
Fractures of Ankle: IV. Clinical Use of Genetic Roentgen Diagnosis and Genetic Reduction. N. Lauge-Hansen.—p. 488.
Radiohumeral Synovitis. M. Moore Jr.—p. 501.
Conservative Treatment of Fractures of Tibial Plateau. C. E. Badgley and S. J. O'Connor.—p. 506.
Surgical Emergencies Resulting from Corpus Luteum Cysts and Hematomas. T. Taniguchi, J. A. Klieger and M. J. Kuhn.—p. 516.

Cardiac Arrest.—Although there has been increasing interest in cardiac arrest, its pathogenesis and the possibilities of its prevention have not received sufficient attention. The "specific tissue" of the heart has no distinguishing anatomic features, but it has the capacity to originate rhythmical contractions autonomously. It is the hardiest tissue in the body, being able to function for long periods without oxygen or even blood supply. The many sources of reflexes that could influence the specific tissue are listed, and the role of anesthesia, anoxia, vitamins of the B group, and endocrine imbalance are discussed. In 35 cases in which a wide variety of anesthetic agents and stimuli were used, 19 patients showed evidence of functional derangements in the specific tissue. At the Lahey Clinic in the last seven years there have been 14 cases of cardiac arrest of such severity as to require surgical intervention, but there must have been many less serious cases that nevertheless represent examples of a vagovagal reflex. The specific tissue that has the capacity to originate stimuli is widely distributed throughout the auricles and ventricles, but there are no vagal fibers in the ventricles. In a normal healthy heart no stimulus from any source, including the carotid sinus, can cause a general collapse, because the specific tissue in the ventricles, being free of vagal influences, can form stimuli and function autonomously. Undesirable reflexes that interfere with the specific tissue may originate in the mucosa of the respiratory or gastrointestinal tracts and in the pleura; those from the pulmonary vessels act on the coronary vessels. Anesthesia depresses the capacity of the specific tissue to form stimuli; in other words, a heart under anesthesia is as vulnerable to vagal stimulation as a heart with widespread organic disease in the specific tissue. Anoxia per se will not cause or initiate these reflexes, but its presence enormously potentiates the action of the anesthetic agent, with a still further depression of the capacity of the specific tissue to form stimuli. Vitamin B complex is important for smooth cardiac function, and in deficient nutrition its adequate use preoperatively is valuable. During endocrine imbalance, such as in the climacteric, substitution therapy is a good preoperative measure. The authors stress that the introduction of various mechanical contrivances into the respiratory or gastrointestinal passages and the clamping or tying of structures containing vagal nerve endings are not without danger, and atropine should be given. In any case in which the surgeon restores cardiac activity after a cardiac arrest, with the possible exception of ventricular fibrillation, the standstill was due to a sudden depression in the automaticity of the specific tissue following a reflex stimulus and almost certainly was preventable.

Alabama State Medical Assn. Journal, Montgomery

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Anaphylactic Reaction from Penicillin: Report of Case. R. K. Wilson. —p. 291.
Thiomerin Further Improved. W. J. Atkinson Jr.—p. 292.

American Heart Journal, St. Louis

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Effect of Induced Ventricular Premature Systoles upon Precordial QRS Pattern in Case of Right Ventricular Hypertrophy. N. O. Fowler, R. N. Westcott, R. C. Scott and J. Taguchi.—p. 521.
*Rare Electrocardiographic Finding Occasionally Seen in Single Ventricle Hearts: Report of Two Cases of Cor Triloculare Biatriatum. A. W. Freireich and G. B. Nicolson.—p. 526.
Electrocardiographic Diagnosis of Acute Cor Pulmonale. M. Eliaser Jr. and F. Giansiracusa.—p. 533.
*Prognostic Significance of Anoxemia Test in Coronary Heart Disease: Follow-up Study of 254 Subjects. J. A. L. Mathers and R. L. Levy. —p. 546.
Importance of Patent Ductus Arteriosus in Infants. R. F. Ziegler. —p. 553.
Unusual Mechanism of Sudden Death in Congenital Heart Disease. F. F. Rosenbaum and F. C. Stiles.—p. 573.
Emetine Therapy and Heart Disease. W. A. Sodeman.—p. 582.
*Comparison of Effects of Veratrum Alkaloids and of Hexamethonium Bromide on Blood Pressure in Arterial Hypertension. F. H. Smirk and O. W. Chapman.—p. 586.
Pulmonary Heart Disease Due to Bilharzia: Bilharzial Cor Pulmonale. Clinical Study of 20 Cases. B. Girgis.—p. 606.

Electrocardiographic Finding in Single Ventricle Hearts.—It is generally agreed that the QRS complex of the electrocardiogram is due to depolarization of the ventricular muscle. The muscle bundles in the ventricle are those of the left ventricle, those of the right ventricle, and those of the interventricular septum. The configuration of the QRS curve depends on the relative size

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Titles marked with an asterisk (*) are abstracted.

of these muscle bundles and the direction of the wave of excitation with respect to the location of the exploring electrode. A heart with a single ventricle with either one or two atriums, can be studied electrocardiographically with respect to the ventricular complex. Freireich and Nicolson studied two patients with a single ventricle. One of these patients is still alive, and the diagnosis of single ventricle was confirmed at operation, in which a subclavian artery was anastomosed to the pulmonary artery. Necropsy in the other patient revealed true cor triloculare biatriatum, with two well-defined atriums, a single large ventricle, and a rudimentary chamber. In the fatal case, the left leg lead was the inverted mirror image of the right arm lead, while in the other case, the left leg lead showed a similar relationship with the left arm lead. This was probably due to the different electrical positions of the single ventricle in relation to the extremities. The ventricular complexes in all the leads consisted of only one or two deflections, a qR, QS, or R.

Anoxemia Test in Coronary Heart Disease.—Mathers and Levy emphasize three points with regard to the anoxemia test: 1. The test should be employed clinically only when the diagnosis is in doubt. 2. A positive result affords objective evidence of coronary insufficiency. 3. A negative result does not rule out the possible presence of coronary heart disease. In order to ascertain the prognostic value of the test, a follow-up study was made of 254 persons on whom it was performed during the decade 1937 to 1947. Included were 141 patients with manifest or suspected coronary heart disease, 10 with hypertension, and 103 with no evidence of a cardiovascular disorder. The average follow-up period was six years. Sixty-three persons died during the course of the study. In the 16 cases in which an autopsy was performed, the clinical diagnosis was confirmed. In an effort to find correlations between the result of the anoxemia test, the clinical status, and the prognosis, a statistical analysis was made, but the results were inconclusive. The cumulative mortality rates of the patients with coronary sclerosis and anginal pain and of the subjects without cardiac symptoms, grouped according to the result of the initial anoxemia test, showed distinct differences. In the patients with coronary disease whose tests were positive, the prognosis was significantly worse with respect to longevity than in those whose tests were negative. It should be emphasized, however, that, whereas this is true for the group as a whole, it does not necessarily apply to any individual patient. The anoxemia test furnishes an index of the coronary reserve only at the time of its performance.

Veratrum Alkaloids versus Hexamethonium Bromide in Hypertension.—In 36 patients with arterial hypertension attempts were made to reduce the blood pressure by oral administration of mixed Veratrum alkaloids. In 27 continued treatment with hexamethonium bromide was also attempted. The blood pressure was reduced substantially without important symptoms in 10 of 36 patients with mixed Veratrum alkaloid therapy and in all of 27 patients with hexamethonium bromide injected subcutaneously. Treatment with hexamethonium was continued for from 1 to 15 months. There seemed no way of predicting without individual trials which patient would respond to Veratrum alkaloids; if, however, the patient was responsive, the blood pressure level throughout the day could usually be well controlled by spacing the doses, though mild toxic symptoms were likely to occur periodically. Moreover, Veratrum alkaloids seemed to be safe in the proper doses, and their hypotensive action was not excessive. Administration is easy, and, if tolerance to the drug does develop, it is very slight. Mixed Veratrum alkaloids seem unsuitable for treatment of acute cardiac complications of hypertension and encephalopathic attacks. Veratrum alkaloids and hexamethonium bromide resemble each other in that the therapeutic range of dosage is narrow. Graded responses can be obtained with less difficulty using hexamethonium bromide. Continued administration leads to drug toleration with hexamethonium bromide, but not with Veratrum alkaloids. The effective dose of hexamethonium bromide becomes stable after some months, and toleration does not interfere with continued treatment. With hexamethonium bromide treatment blood pressure falls are greatest in the standing, intermediate in the sitting, and least in the prone posture. After ingestion of Veratrum alkaloids postural hypotension is inconspicuous. After ingestion of hexamethonium bromide the pulse is ordinarily accelerated, but following continued treatment it may be unchanged. Bradycardia occurs with Veratrum alkaloid therapy. The main toxic manifestation of hexamethonium bromide is faintness and lassitude associated with excessive fall of blood pressure; the symptoms are maximal when the blood pressure is at its lowest level. Toxic effects of the Veratrum alkaloids occur while the blood pressure is still falling, and may disappear before the blood pressure reaches its lowest level.

American Journal of Hygiene, Baltimore

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Studies on Plasmodium Gallinaceum: II. Factors in Blood of Vertebrate Host Influencing Mosquito Infection. D. E. Eyles.—p. 276.
Studies on Poliomyelitis Viruses in Cultures of Monkey Testicular Tissue. J. S. Youngner, E. N. Ward and J. E. Salk.—p. 291.

Effect of Pasteurization on Coxiella Burnetii.—The effect of pasteurization on the survival of Coxiella burnetii was investigated. Pasteurization was carried out in commercial processing plants under routine conditions. In 1 of 35 instances the organism survived pasteurization by the vat-holding method; in this instance, however, pasteurization, as judged by the phosphatase test, may not have been complete. In 2 instances of 42 the organisms were detected in milk pasteurized by the high temperature and short time method. In an addendum to this report the authors state that after this paper had been prepared for publication, there came to their attention the report of Marmion and his associates on "The Effect of Pasteurization on Milk Containing Rickettsia Burneti," (*Monthly Bull. Ministry of Health and the Pub. Health Lab. Service* **10:**119-128, 1951). These workers found that treatment of naturally infected milk at 154 to 156 F for 15 seconds was sufficient to render the milk noninfective for guinea pigs. On the other hand, artificially infected milk containing large numbers of rickettsiae still possessed infectivity after treatment at 158 to 159 F for 15 seconds, but was rendered noninfective after treatment at 161 F for 15 seconds.

American Journal of Medicine, New York

12:379-498 (April) 1952

Cerebral Circulation and Metabolism in Chronic Pulmonary Emphysema, With Observations on Effects of Inhalation of Oxygen. J. L. Patterson Jr., A. Heyman and T. W. Duke.—p. 382.
Pulmonary Function in Patients Convalescing from Acute Poliomyelitis with Respiratory Paralysis. D. S. Lukas and F. Plum.—p. 388.
Venous Thrombosis in Upper Extremities as Complication of Myocardial Failure. W. E. Loring.—p. 397.
Pulmonary Infarction Complicating Thrombophlebitis of Upper Extremity. C. E. Tomlin.—p. 411.
*Some Supravital Observations on "L. E." Phenomenon. R. J. Rohn and W. H. Bond.—p. 422.
Effectiveness of Various Drugs for Prophylaxis of Seasickness. H. I. Chinn, S. W. Handford, T. E. Cone Jr. and P. K. Smith.—p. 433.
Study of Therapeutic Effects of Some Amebacidal Drugs. W. A. Sodeman and P. C. Beaver.—p. 440.

Supravital Observations on "L. E." Phenomenon.—After reviewing the current literature on the "L. E." cell phenomenon, Rohn and Bond present their method for obtaining, preparing, and supravitally staining peripheral blood and bone marrow

specimens. Using this technique they examined approximately 5,000 peripheral blood and 800 bone marrow specimens of patients referred to a hematology service during one year. They demonstrated L. E. cells in five patients. They found that the L. E. cell has two component parts. The L. E. cell inclusion body was always a mature, autolyzed polymorphonuclear neutrophil. The phagocytic cell was either a mature polymorphonuclear neutrophilic, eosinophilic, or basophilic leukocyte, with the neutrophilic leukocytes overwhelmingly predominating. Bone marrow examination proved the most reliable means of demonstrating L. E. cells by their technique, even though, on routine examination, they found L. E. cells in the peripheral blood in four of the five summarized cases. The authors regard this as a simple, effective, direct method for demonstrating L. E. cells without special procedures on peripheral blood or bone marrow.

Annals of Internal Medicine, Lancaster, Pa.

36:933-1156 (April) 1952

*Morphology and Pathogenesis of Cardiac Fibrosis of Liver. E. Moschcowitz.—p. 933.

Diverticula of Gastrointestinal Tract. M. A. Gold and J. G. Sawyer.—p. 956.

Provocative Serological Reaction in Late Syphilis: Its Relation to Technical Factors. R. W. Maxwell and V. Scott.—p. 979.

*Cortisone and Gold Therapy in Chronic Rheumatoid Arthritis. H. E. Thompson and H. J. Rowe.—p. 992.

Acute Severe Upper Gastrointestinal Hemorrhage: Review of 195 Cases. J. R. Gott Jr., E. L. Smith and D. D. Dornan.—p. 1001.

Pyelonephritis Lenta. O. Saphir and B. Taylor.—p. 1017.

Diagnostic Problems of Rheumatic Fever and Their Impact on Management of Rheumatic Fever Patient. F. J. Lewy.—p. 1042.

*Soft Tissue Calcification, with Special Reference to Its Occurrence in "Collagen Diseases." G. E. Wheeler, A. C. Curtis, E. P. Cawley and others.—p. 1050.

Oral Use of Combined Vitamin B_{12} and Folic Acid in Tropical Sprue. F. Diéz Rivas, F. Hernández Morales and L. M. Meyer.—p. 1076.

Effect of Penicillin on Renal Lesions of Subacute Bacterial Endocarditis. D. M. Spain and D. W. King.—p. 1086.

Hepatic Fibrosis in Cardiac Disease.—Moschcowitz prefers the term fibrosis to cirrhosis, and points out that there are widely differing opinions concerning the morphology and pathogenesis of hepatic lesions associated with cardiac disease. The earliest phase in the development of this condition is that characterized by what is usually referred to as "nutmeg" liver, in which there is dilatation of the central sinusoids with trabecular narrowing. Later, centrolobular necrosis ensues. Thereafter, the morphological changes depend on whether hypertension of the portal circulation is maintained long enough. This usually occurs in constrictive pericarditis, often in the terminal stages of tricuspid valve disease. That portal hypertension is maintained was shown by histological demonstration of "congestive splenomegaly." Under such circumstances, various forms of fibrosis occur: first, capillary sclerosis around the central veins; second, organization of the centrolobular necrotic areas with the development of new central veins in these fibrotic areas, either by autochthonous formation of capillaries or by direct sprouts from the terminal branches of the portal vein in the interlobular septa; and third, by sclerosis of the hepatic veins and the immediately adjacent parenchyma. The periportal fibrosis that has been described as occurring in "cardiac cirrhosis" bears no resemblance to that observed in true Laennec's cirrhosis. Cardiac fibrosis is not a replacement fibrosis but is an active and proliferative process. New capillary shunts or short circuits are developed simultaneously. There are four kinds of such shunts: first, between the terminations of the portal vein and the central vein in the interlobular septa; second, by newly formed capillaries that bud from the terminal branches of the portal veins within the portal septa to the central veins; third, by budding from the preexisting portal branches in the interlobular septa to the newly formed central veins; and fourth, by direct capillary communication between the terminations of the portal veins in the interlobular septa and the hepatic veins. These shunts are compensatory mechanisms to help equalize the pressures between the portal vein and the hepatic veins. Evidence is submitted that the morphological changes of cardiac fibrosis are the result of portal hypertension of central origin. Advanced hepatic cirrhosis may be suspected if there is constrictive pericarditis of long duration, persistent and recurring ascites, increased peripheral venous pressure, splenomegaly, and enlargement of right auricle and ventricle, and dilatation of the pulmonary artery.

Cortisone and Gold in Chronic Rheumatoid Arthritis.—A total of 92 patients with active chronic rheumatoid arthritis were divided into four series: first, eight patients who had been receiving gold with only moderate benefit were given cortisone in addition; second, 13 patients were given gold and cortisone concurrently; third, 42 patients were given gold alone; and fourth, 29 patients were given cortisone alone. For comparison, 273 patients who received neither gold nor cortisone were restudied. The dosage levels were as follows: Cortisone was given in doses of 100 mg. intramuscularly every eight hours for 24 hours, then every 12 hours for 24 hours, and then 100 mg. daily for 21 days. Then cortisone therapy was discontinued until a relapse occurred. It was then reinstituted at the previous level and, after 14 days, 75 to 100 mg. were given every other day parenterally, or 50 to 75 mg. per day orally. Administration of cortisone was then again discontinued. Gold was given in initial doses of 10 mg. either intramuscularly or intravenously, and then at weekly intervals in 50 mg. doses until a total of 1 gm. had been given. Administration of gold was then continued at 10, 14, 21, and 30 day intervals. The authors gained the impression that gold given to patients with active chronic rheumatoid arthritis with moderate benefit apparently had no additional effect when cortisone was added. Despite an excellent therapeutic response, no complete remissions were observed in this group of eight patients, and they returned to their precortisone state shortly after administration of the hormone was discontinued. Gold given concurrently with cortisone seemed to arrest rheumatoid arthritis in approximately the same percentage of patients as gold given alone, but it appeared superior to cortisone employed alone, and to therapy without gold or cortisone. Gold and cortisone administered concurrently gave an immediate increase in functional capacity, and in some patients it produced a complete remission. These effects continued in a number of patients when cortisone was discontinued. In addition, the concurrent administration of gold and cortisone has several therapeutic advantages: first, patients who have previously been intolerant to gold can be given gold with cortisone with less danger of a reaction (to gold). Second, with cortisone rehabilitative measures can be carried out before the gold levels are sufficiently high to be effective. Third, administration of cortisone may be discontinued in the patients who respond to gold.

Soft Tissue Calcification.—The term calcinosis circumscripta and calcinosis universalis imply the deposition of calcium salts in skin and subcutaneous tissue. Much of the confusion and mystery surrounding the use of the terms calcinosis circumscripta and calcinosis universalis stems from the practice of regarding calcification as a primary process, whereas careful study will always reveal a primary disease responsible for the calcification. This report is concerned with the 54 instances of calcinosis of the circumscript or universal varieties reported in the literature since 1938 and 12 cases of several types of collagen disease studied by Wheeler and associates at the University of Michigan Hospital. Detailed reports are given of two of the latter 12 patients and brief reports of the other 10. A table that lists the primary diagnoses of all the 66 patients with calcinosis of the circumscript or universal varieties shows that most patients had scleroderma, Raynaud's syndrome, or dermatomyositis. Thirty-four of the patients are in the scleroderma group and 32 in the dermatomyositis group. In general, serum calcium, phosphorus, and alkaline phosphatase determinations are reported as normal in collagen diseases associated with calcification, but it is suggested that possibly calcium is being removed from the blood and stored in injured tissue. Calcification may be secondary to a disturbance of factors regulating blood serum calcium and/or phosphorus levels. It may also occur in the so-called collagen diseases as a result of tissue injury. The following diseases should be considered when calcinosis is found: scleroderma, dermatomyositis, Raynaud's syndrome, rheumatoid arthritis, acrodermatitis chronica atrophicans, hyperparathyroidism, vitamin D intoxication, metastatic bone

disease, multiple myeloma, Paget's disease of bone, renal failure, and pseudohypoparathyroidism. A table lists the results of laboratory tests and roentgenograms of the skeletal system to be expected in these conditions.

Annals of Surgery, Philadelphia

135:433-576 (April) 1952

Relation of Gastric Secretion to Events Following Pyloric Obstruction. J. S. Clarke, H. A. Oberhelman Jr., S. O. Evans and L. R. Dragstedt. —p. 433.
*Electrolyte Abnormalities in Pyloric Obstruction Resulting from Peptic Ulcer or Gastric Carcinoma. H. S. Lans, I. F. Stein Jr. and K. A. Meyer.—p. 441.
*Response of Dicumarol-Induced Hypoprothrombinemia to Vitamin K_1. A. Rehbein, A. Jaretzki III and D. V. Habif.—p. 454.
Intravascular Agglutination and Vascular Stasis in Peptic Ulceration. J. A. Key.—p. 470.
Local Use of Streptokinase-Streptodornase in Chronic Refractory Areas of Suppuration with Draining Sinuses. S. Sherry and W. S. Tillett. —p. 479.
Cancer of Tongue. D. Lyall and C. F. Schetlin.—p. 489.
Results of Total Gastrectomy for Cancer of Stomach. J. P. West and J. R. Fenger.—p. 497.
Compound Wounds of Hand. J. E. Flynn.—p. 500.
Congenital Dislocation of Hip: Technic of Open Reduction. M. B. Howorth.—p. 508.
Radical Ilio-Inguinal Lymphatic Excision. A. P. Hovnanian.—p. 520.
Management of Foreign Bodies in Alimentary Tract. T. D. Grekin and M. M. Musselman.—p. 528.
Hypersplenism: Review and Case Report. R. V. Schatken.—p. 536.
Arrhenoblastoma of Ovary: Report of Three Cases. C. Y. Thomas Jr., E. R. Fisher, R. B. Turnbull and J. S. Krieger.—p. 543.
Proliferative Cysts of Pancreas. K. C. Sawyer, J. R. Spencer and A. E. Lubchenco.—p. 549.
Ileal Duplications. M. P. Fecher, S. M. Day and F. G. King.—p. 555.
Perforation of Sigmoid Colon During Barium Enema: Report of Case with Review of Literature, and Experimental Study of Effect of Barium Sulfate Injected Intraperitoneally. L. J. Kleinsasser and H. Warshaw. —p. 560.
Congenital Atresia of Esophagus with Tracheo-Esophageal Fistula, Duodenal Atresia, and Other Anomalies: Case Report. W. C. McGarity, O. A. Abbott and L. W. Grove.—p. 566.
Intraperitoneal Rupture of Iliac Aneurysm with Survival Following Surgical Treatment: Report of Case. P. A. Fernbach, L. Berman and B. Cohen.—p. 570.

Electrolyte Abnormalities in Pyloric Obstruction.—Prolonged untreated illness and protracted use of potassium-free intravenous fluids may result in electrolyte imbalances. The loss of sodium and chloride accompanying vomiting is well known, and recent studies have shown that a considerable amount of potassium may also be lost as a result of vomiting or prolonged gastric suction. Patients with gastric carcinoma or vagotomy may have alkalosis, hypochloremia, and hypopotassemia, because high concentrations of chloride and potassium ions may be present in the gastric contents in spite of the absence of titratable hydrochloric acid. Analysis of the gastric contents in patients with pyloric obstruction shows that their daily potassium loss may equal from 6 to 8 gm. of potassium chloride. The loss of chloride exceeds that of sodium when the obstruction is due to peptic ulcer, because free hydrochloric acid is present in the gastric juice; this leads to hypochloremia and alkalosis. Gastric resection, on the contrary, usually results in a loss of sodium exceeding that of chloride, leading to acidosis. Hypochloremia and alkalosis resistant to isotonic sodium chloride solution may be corrected by intravenous potassium chloride therapy. The addition of 3 gm. of potassium chloride to a liter of isotonic sodium chloride solution, amino acids, or 5% dextrose solution provides potassium and chloride ions in excess of sodium, resulting in an increase of intracellular potassium and extracellular chloride. Such solutions should be administered at the rate of from 120 to 180 drops a minute; faster administration may lead to a high serum potassium level, which is toxic to the heart and may cause heart block and cardiac arrest. Potassium must be given cautiously to patients with renal insufficiency or dehydration. Parenteral potassium therapy is not needed after the patient is able to eat, because most foods are good sources of potassium. This treatment resulted in a striking improvement in the mental attitude and muscular strength of all patients; 14 were in critical condition when it was begun, but all responded to therapy and there were no deaths.

Response of Bishydroxycoumarin-Induced Hypoprothrombinemia to Vitamin K_1.—Vitamin K_1 in the form of an emulsion may safely be given intravenously. It has proved effective in reversing hypoprothrombinemia due to bishydroxycoumarin (dicumarol®) and other prothrombin-depressing drugs, returning the prothrombin time to normal or nearly normal levels in approximately six hours irrespective of the degree of hypoprothrombinemia and the amount of recently administered bishydroxycoumarin. The response to a dose of 50 mg. was as prompt and effective as it was to larger doses; when a 50 mg. dose was given, resistance to subsequent doses of bishydroxycoumarin did not develop. The fact that vitamin K_1 controls bleeding by correcting the coagulation defect more rapidly than any other agent makes the use of whole blood and plasma unnecessary except when blood volume replacement is required. Vitamin K_1 is also valuable in reversing hypoprothrombinemia immediately before operation, and in reducing excessive hypoprothrombinemia not accompanied by bleeding to a therapeutic level so that anticoagulant therapy may continue without interruption. For the latter purpose doses of from 0.5 to 2.5 mg. of vitamin K_1 given intravenously will reverse the prothrombin time rapidly, returning it in most instances to a safe but still therapeutic level in from three to six hours when average doses of bishydroxycoumarin have resulted in excessively high levels.

Diseases of Chest, Chicago

21:245-368 (March) 1952

Use of Trypsin in Chest Disease. L. C. Roettig, H. G. Reiser, W. Habeeb and L. Mark.—p. 245.
Primary Pulmonary Tuberculosis as Cause of Bronchiectasis in Children. L. B. Dickey.—p. 260.
Detection and Identification of Intracardiac Calcifications. J. E. Habbe. —p. 268.
Evaluation of Ioduron B in Bronchography: I. Preliminary Study on Animal Tissues. W. Hentel, M. B. Cohen and L. C. Brandenstein. —p. 280.
Id.: II. Preliminary Study in Man. M. B. Cohen, W. Hentel and L. C. Brandenstein.—p. 286.
Lung Immobilization Chamber Therapy in Chronic Pulmonary Tuberculosis (with Case Reports). W. Grosfeld and J. C. Nash.—p. 296.
Pathogenesis of So-Called Idiopathic Spontaneous Pneumothorax and Related Conditions. A. Sattler.—p. 315.
Bronchial Onset of Reinfection Tuberculosis in the Adult. J. J. Castillo. —p. 320.
Pneumonia Associated with Ingestion of Petroleum Products by Children. M. L. Podolsky.—p. 327.
Epiphrenic Diverticulum of Esophagus: Review of Its Surgical Treatment and Report of Case. H. W. Kausel and G. E. Lindskog.—p. 334.
Pulmonary Histoplasmosis: Report of Case Long Considered Tuberculous Improved by Acti-Dione. H. M. Wilson and A. W. Duryea.—p. 346.

21:369-490 (April) 1952

On Lasting Protective Effect of Hydrazine Derivatives of Isonicotinic Acid in Experimental Tuberculosis Infection of Mice. E. Grunberg, B. Leiwant, I.-L. D'Ascensio and R. J. Schnitzer.—p. 369.
Tolerance of Macacus Rhesus for Isonicotinylhydrazines: Preliminary Report. R. A. Lewis and I. Zieper.—p. 378.
*Tuberculosis Chemotherapy with Hydrazine Derivatives of Isonicotinic Acid. I. J. Selikoff and E. H. Robitzek.—p. 385.
Determination of Blood Plasma Levels of Hydrazine Derivatives of Isonicotinic Acid. S. H. Rubin, L. Drekter, J. Scheiner and E. De Ritter. —p. 439.
Chloramphenicol in Control of Bronchopulmonary Suppuration. M. S. Harris, L. Gornell, C. Shore and H. Lovitz.—p. 450.
Chronic Friedlander's Pulmonary Infection Treated with Chloromycetin: Case Report. H. Steinberg and M. N. Towbin.—p. 455.
Pulmonary or Bronchial Lavage and Simultaneous Tomographies. M. de Abreu.—p. 460.
Tuberculous Empyema Treated with Streptokinase-Streptodornase: Report of Case with Cure. A. Goldman.—p. 478.

Hydrazine Derivatives of Isonicotinic Acid in Tuberculosis.—The authors report results of treatment with the hydrazide of isonicotinic acid ("rimifon") and its isopropyl derivative ("marsilid") in 92 patients with moderately or far-advanced pulmonary tuberculosis. All patients had positive sputum and active disease before institution of therapy; 45 were toxic and febrile. Patients, divided into groups, were treated with 2, 4, and 10 mg. per kilogram of "marsilid" and 4 mg. of "rimifon" for from 4 to 15 weeks. Fever and toxicity disappeared within two to three weeks in all cases. Improvement in appetite and in sense of well-being was associated with weight gains, which were as great as 64 lb. (29 kg.) and averaged 18 lb. (8.2 kg.) in nine weeks of treatment. The sputum became negative in 25% of patients and in an-

other 28% sputum that had been consistently positive became "occasionally positive." Cough and expectoration disappeared completely or almost so in from two to three weeks. Cavity closure occurred in 2 cases, marked reduction in cavity size was noted in 33 cases, and clearing of exudate occurred 17 times. In four cases the exudate became more extensive, and in one case a new cavity seemed to form where exudate had been present before treatment. Cure or great improvement was observed in patients with tuberculous laryngitis, otitis, or glossitis. Toxic effects of marsilid and rimifon therapy included hyperreflexia, leg-twitching, constipation, vertigo, and reflex disturbance of micturition. No fatality resulted from use of these drugs, and every patient was benefited.

Endocrinology, Springfield, Ill.

50:143-276 (Feb.) 1952. **Partial Index**

Effect of Alloxan Diabetes on Response of Adrenal Gland to Cold Stress. S. J. Shepherd Jr., M. J. Smith and B. B. Longwell.—p. 143.
Quantitative Method for Bioassay of Effect of Adrenal Cortical Steroids on Mineral Metabolism. S. A. Simpson and J. F. Tait.—p. 150.
Effects of Purified Gonadotrophins on Cholesterol Content of Testes of Immature Rats. J. Tepperman and H. M. Tepperman.—p. 162.
Protein-Bound Iodine in Various Tissues After Injection of Elemental Iodine. H. M. Klitgaard, H. B. Dirks Jr., W. R. Garlick and S. B. Barker.—p. 170.
Acute Effect of Adrenal Cortical Extract, Adrenocorticotropic Hormone, and Desoxycorticosterone Acetate on Thiocyanate, Bromide, and Mannitol Spaces; Plasma Volume and Total Body Water in Normal Dogs. J. M. B. Bloodworth Jr.—p. 174.
Enhancement of Adrenocorticotropic Hormone Activity by Alum in Normal 21-Day Old Male Rats. T. Hayashida and Choh Hao Li.—p. 187.
Effects of Thyroid and of Choline and Inositol on Cholesterol Distribution in Rats Fed High Cholesterol Diet. S. B. Weiss, L. Marx and W. Marx.—p. 192.
Water Excretion in Hypophysectomized Rats Before and After Adrenalectomy. F. G. Hofmann.—p. 206.
Response to Alloxan Modified by Gonadectomy. E. F. Beach, P. J. Bradshaw and N. R. Blatherwick.—p. 212.
Problem of Placental Permeability for Thyrotrophin, Propylthiouracil and Thyroxine in Guinea Pig. R. R. Peterson and W. C. Young.—p. 218.
On Extra-Adrenal Actions of Adrenocorticotrophic Preparations. B. Jacot and H. Selye.—p. 254.
Cytochemical Study of Adrenal Cortex of Rat with Experimental Cardiac Hypertrophy. H. Bacchus, M. H. Heiffer and N. Altszuler.—p. 264.

Journal of Bone and Joint Surgery, Boston

34A:249-504 (April) 1952. **Partial Index**

The Surgical Experiment. J. S. Barr.—p. 249.

SYMPOSIUM: STREPTOMYCIN IN TREATMENT OF BONE AND JOINT TUBERCULOSIS

Streptomycin in Bone and Joint Tuberculosis. D. M. Bosworth and H. A. Wright.—p. 255.
Tuberculosis of Bones and Joints, with Special Reference to Influence of Streptomycin and Application of Radical Surgical Techniques to Certain Effects and Complications of Tuberculous Lesion. E. T. Evans.—p. 267.
Streptomycin in Treatment of Bone and Joint Tuberculosis. R. I. Harris, H. S. Coulthard and F. P. Dewar.—p. 279.
*Evaluation of Streptomycin Therapy in Controlled Series of Ninety Cases of Skeletal Tuberculosis. Public Health Service Cooperative Investigation.—p. 288.
*Treatment of Tuberculous Bone Disease by Surgical Drainage Combined with Streptomycin. M. S. DeRoy and H. Fisher.—p. 299.
Tear of Sacrospinous and Sacrotuberous Ligaments. M. Burman.—p. 331.
Para-Articular Calcification and Ossification Following Acute Anterior Poliomyelitis in an Adult. J. A. Freiberg.—p. 339.
Congenital Kyphoscoliotic Tibia. C. E. Badgley, S. J. O'Connor and D. F. Kudner.—p. 349.
Giant-Cell Tumor of Bone. M. J. Stewart and T. R. Richardson.—p. 372.
Thorn-Induced "Tumors" of Bone. D. J. Maylahn.—p. 386.
Electron-Microscopic Study of Crystalline Inorganic Component of Bone and Its Relationship to Organic Matrix. R. A. Robinson.—p. 389.
Patellar Graft for Severely Depressed Comminuted Fractures of Lateral Tibial Condyle. W. J. Wilson and J. E. Jacobs.—p. 436.
Osteogenetic Potency and New-Bone Formation by Induction in Transplants to Anterior Chamber of Eye. M. R. Urist and F. C. McLean.—p. 443.
Sensory Nerves of Hip Joint. L. G. Wertheimer.—p. 477.
Surgical Approach for Neuroma of Plantar Digital Nerve (Morton's Metatarsalgia). D. C. McKeever.—p. 490.
Incidence of Separate Neural Arch and Coincident Bone Variations. M. B. Roche and G. G. Rowe.—p. 491.

Streptomycin in Skeletal Tuberculosis.—Of 90 patients with skeletal tuberculosis observed for 15 months, 50 were given at least one course of streptomycin with daily intramuscular doses of 20 mg. per kilogram of body weight for 91 days, while 40 were not treated with streptomycin. The small number of patients in the streptomycin and control groups limits the conclusions that may be drawn from the authors' observations, which are as follows: 1. On the basis of x-ray evidence alone, the condition of the patients in the streptomycin-treated and in the control groups was essentially the same; more than four-fifths of the patients in each group showed improvement roentgenographically at the end of 15 months. 2. On the basis of the patients' condition as judged by x-ray and clinical data combined, there was more improvement in the streptomycin-treated patients. At 15 months only 28 of the 40 patients in the control group showed improvement, whereas improvement was noted in 38 of the 50 streptomycin-treated patients as early as three months, and in 41 patients of this group at 15 months. 3. Streptomycin appears to produce a generalized effect on the well-being of the patient with skeletal tuberculosis and on the secondary manifestations of the tuberculous process, as illustrated by cessation of sinus drainage, reduction in the sedimentation rate, return towards a normal hemoglobin level, and evidence of greater improvement in functional ability. The data appear to substantiate the hypothesis that because of the relative avascularity of bone lesions and because a tuberculous focus is usually isolated by fibrous tissue walls, little streptomycin reaches the skeletal lesion. Hence the roentgenographic evidence of progress is quite similar for the streptomycin and control groups. However, streptomycin may ameliorate the toxic effects of the tubercle bacillus, and, in contiguous areas where the vascular supply is better, may decrease the spread of the disease process and bring about improvement in the general condition. Clinically patients treated with streptomycin were in a better condition than the control patients.

Surgical Drainage Combined with Streptomycin in Tuberculous Bone Disease.—Treatment with streptomycin in doses of 1 gm. per day intramuscularly in conjunction with the surgical incision of abscesses, débridement of lesions, and their conversion to freely draining sinuses by the use of gauze packing was practiced between October, 1946, and April, 1950, in 52 patients between the ages of 1 and 72 years who had 63 closed tuberculous bone lesions. Excellent results were obtained in 37 of the 52 patients, with cessation of bone and joint destruction, closure of all sinuses, absence of pain, retention of 75% or more of active peripheral joint motion or solid surgical fusion when performed, no recurrence of drainage, and improvement in general health. Thirteen patients obtained good results, with cessation of bone and joint destruction, closure of all sinuses, relief of pain, retention of 25 to 75% of active peripheral joint motion, recurrence of slight drainage (additional streptomycin being required for closure), and improvement in general condition. Two patients died, one 18 months after operation, of tuberculosis of the kidney and lungs and amyloid disease, although the bone lesions were healed. The other died of amyloid disease and destruction of the kidneys 37 months after operation. Although the series is small and the average follow-up period of three and a half years is short, the following preliminary conclusions may be drawn: Following adequate surgical drainage and treatment with streptomycin, destruction from bone and joint tuberculosis ceased, and roentgenograms showed evidence of recalcification and apparent regeneration of bone. There was no tendency toward reactivation of the lesion, clinically or symptomatically. In the surgically produced sinuses, subsidence of drainage and closure in from 3 to 16 weeks occurred. Although the surgically treated lesions will heal clinically, new lesions in other parts of the body may develop and progress, despite administration of streptomycin. Bone tends to regenerate in children, with re-establishment of an apparently normal epiphyseal plate and no disturbance in the rate of growth. A good functional range of motion was the usual end result, even when there was roentgenographic evidence of extensive destruction of the joint. The factor of secondary infection was apparently of no consequence in the arrest and healing of these lesions.

J. Bowman Gray School Med., Winston-Salem, N. C.

10:27-56 (April) 1952

*Potassium Deficiency States and Their Clinical Management. H. H. Cook Jr.—p. 27.
Effects of Hepatic Factors on Peripheral Vascular System. C. McMillan. —p. 38.

Potassium Deficiency.—Reviewing the present status of knowledge on potassium deficiency, Cook stresses that it is a common disorder and should be suspected any time oral feeding is diminished sharply or discontinued with continued urinary excretion or there is persistent loss of gastrointestinal secretions in any form, and in diabetic acidosis and coma. Potassium deficiency also occurs in digitalis intoxication, with adrenocortical substitution therapy (including administration of corticotropin), in familial periodic paralysis, and in bulbar poliomyelitis, and is of particular importance in the latter where there is usually a marked decrease in respiratory reserve. The symptoms associated with hypopotassemia are nonspecific but usually include weakness, drowsiness, langour, hypotonia of the skeletal muscles, dyspnea with gasping respiration, cyanosis, nausea, vomiting and occasionally mild sensory disturbances in the form of mild paresthesias. The diagnosis depends not so much on the symptomatology as on recognition of situations in which potassium deficiency is likely to occur. The electrocardiogram is the most practical adjunct to the clinical impression. Typical electrocardiographic changes are prolongation of the Q-T interval. The T wave is decreased in amplitude and ultimately inverted. The S-T segment sags, and the S-T takeoff is depressed. These signs are exactly opposite to those characteristic of potassium intoxication. In the treatment of potassium deficiency the oral route is preferred, and potassium chloride is probably the best drug. There is no danger from oral potassium therapy in patients with good renal function, but adequate laboratory facilities should be available when potassium is administered intravenously.

Journal Clin. Endocrin. & Metab., Springfield, Ill.

12:257-370 (March) 1952

*Further Studies on Treatment of Congenital Adrenal Hyperplasia with Cortisone: I. Comparison of Oral and Intramuscular Administration of Cortisone, with Note on Suppressive Action of Compound F and B on Adrenal. L. Wilkins, L. I. Gardner, J. F. Crigler Jr. and others. —p. 257.
*Id.: II. Effects of Cortisone on Sexual and Somatic Development, with Hypothesis Concerning Mechanism of Feminization. L. Wilkins, J. F. Crigler Jr., S. H. Silverman and others.—p. 277.
Adrenal Cortical Function in Hypertension. B. S. Hetzel and D. C. Hine. —p. 296.
Action of Estrogen and Progesterone on Gonadotropin Content of Pituitary of Monkey (Macaca Mulatta). H. A. Salhanick, F. L. Hisaw and M. X. Zarrow.—p. 310.
Effects of Chorionic Gonadotropin and Prolactin on Maintenance of Corpus Luteum Function. P. H. Fried and A. E. Rakoff.—p. 321.
Acid Phosphatase Concentration of Prostatic Exprimate During Normal Puberty. J. E. Kirk, A. Eisenstein and C. M. MacBryde.—p. 338.
Effect of Cortisone on Tolerance to Ascorbic Acid and Level of Blood Cholesterol in Man. W. M. Booker, J. B. Johnson, R. L. Hayes and others.—p. 346.
Studies on Mechanism of Spermatic Release of Male North American Frog (Rana Pipiens): Reaction to Various Hormones. S. L. Robbins and F. Parker Jr.—p. 354.

Cortisone in Congenital Adrenal Hyperplasia.—Eleven patients with congenital adrenal hyperplasia were treated continuously with cortisone for from five to 17 months. Six were female pseudohermaphrodites between the ages of 8½ and 18½ years, three were female pseudohermaphrodites, between 11 and 19 weeks of age when treatment was started, with defects of electrolyte regulation and two were boys with macrogenitosomia praecox, aged 4½ and 7 years. As a result of their experience with these patients, the authors make the following tentative suggestions: To obtain rapid suppression of the abnormal androgenic activity of the patient's adrenals, initial treatment with relatively large doses of intramuscular cortisone may be given. For patients eight years of age or over, 50 mg. of cortisone intramuscularly per day are adequate; in infants, 25 mg. per day. It seems preferable to begin treatment with cortisone intramuscularly rather than orally, because the results are more predictable. The maximum suppression of urinary ketosteroids should be attained within 5 to 10 days, after which the maintenance dose should be determined. For patients over 8 years of age the maintenance dose of cortisone given intramuscularly is usually 25 mg. per day. Doses of 75 mg. of cortisone every third day or 100 mg. every fourth day are just as effective. When cortisone is given orally doses of 50 or 75 mg. per day are required. These amounts should be given in equally divided doses, two, three, or four times a day. For young infants the maintenance dose of cortisone is smaller. In the authors' patients, intramuscular injections of 5 mg. daily and of 25 mg. every fourth day and oral doses of 5 mg. and 12.5 mg. per day seemed to maintain suppression, but larger amounts may be required in some cases. For children between the ages of 1 and 8 years, the maintenance dose is probably somewhere between these amounts and 25 mg. per day, when the drug is given intramuscularly. It should be determined individually for each patient. The effects of intramuscular medication seem to be more predictable, probably because of the more uniform rate of absorption. In young infants who have the sodium-losing type of congenital adrenal hyperplasia, it is important that treatment include a high sodium intake and/or desoxycorticosterone in addition to cortisone. In the one patient who was given compound F (17-hydroxycorticosterone) in doses of 25 mg. per day, it seemed to have approximately the same effect as cortisone on the suppression of adrenal activity. In an infant with the salt-losing type of adrenal hyperplasia, compound B (corticosterone) seemed to have somewhat less suppressive action than cortisone, but a definite sodium-retaining effect was exerted by doses of 12.5 mg. per day. The ultimate effects on the adrenal of the amounts of cortisone administered are not known. Although cortisone seemed to suppress the response of the adrenal to 24 hour tests with corticotropin (ACTH), the activity of the adrenals as measured by the 17-ketosteroid excretion returned promptly when cortisone was discontinued after 227 days of continuous therapy.

Effects of Cortisone on Sexual and Somatic Development.—The effects of cortisone on sexual and somatic development were studied in the 11 patients with congenital adrenal hyperplasia who were treated continuously with this drug for 5 to 17 months as reported in the preceding paper. In all six girls between the ages of 8½ and 18½ years the breasts promptly developed and the vaginal smears showed estrinization. Three of these patients have menstruated regularly. There has been an unquestionable decrease of hirsutism in all patients, and in two the decrease was quite pronounced. To obtain the most satisfactory results, it is essential to give the minimum amount of cortisone necessary to maintain the excretion of 17-ketosteroids below 8 mg. per day in the older patients, as recurrence of androgenic manifestations was observed when larger amounts of ketosteroids were excreted. In one infant, 25 mg. of intramuscular cortisone daily inhibited growth and osseous development, while 5 mg. suppressed excessive androgen secretion without inhibiting normal growth. During childhood it is advisable to follow both the urinary 17-ketosteroids and the rates of growth and osseous development as guides to treatment. The minimal effective dose of cortisone and the level at which the urinary 17-ketosteroids should be maintained must be determined individually in each case. In one of the two boys with macrogenitosomia praecox, cortisone led to adolescent development and growth of the patient's testes, suggesting that normal maturation was occurring. The rapid female sexual development in three pseudohermaphrodites between 8½ and 10½ years old and the testicular development in a boy aged 7 may be due to the fact that these patients had attained a somatic and osseous development of from 13 to 15 years, owing to the accelerating effects of excessive androgen. Apparently the pituitary-gonadal mechanism had matured enough to be capable of functioning promptly as soon as the inhibiting effects of adrenal hormones were suppressed.

Journal of Clinical Investigation, Cincinnati

31:245-340 (March) 1952

Responses to Painful Stimuli of Patients with Severe Chronic Painful Conditions. M. A. Kennard.—p. 245.
Diurnal Variation in Urinary Excretion of Neutral Lipid-Soluble Reducing Steroids in Congestive Cardiac Failure and Cirrhosis of Liver with Ascites. R. Goldman and S. H. Bassett.—p. 253.
Effects of Potent Analgesics upon Vestibular Function. L. B. Gutner, W. J. Gould and R. C. Batterman.—p. 259.
Effect of Theophylline with Ethylenediamine (Aminophylline) on Cerebral Hemodynamics in Presence of Cardiac Failure With and Without Cheyne-Stokes Respiration. J. H. Moyer, S. I. Miller, A. B. Tashnek and R. Bowman.—p. 267.
Effects of *l*-Epinephrine and *l*-Nor-Epinephrine upon Cerebral Circulation and Metabolism in Man. B. D. King, L. Sokoloff and R. L. Wechsler.—p. 273.
Volume of Distribution of Sodium Thiosulfate as Measure of Extracellular Fluid Space. R. H. Cardozo and I. S. Edelman.—p. 280.
Electrolyte Content of Skeletal Muscle in Congestive Heart Failure: Comparison of Results with Inulin and Chloride as Reference Standards for Extracellular Water. R. Mokotoff, G. Ross and F. Leiter. —p. 291.
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Comparison of Allantoin and Inulin Clearances for Measurement of Filtration Rate in Diseased Human Kidney. B. F. Miller, A. Leaf, A. R. Mamby and Z. Miller.—p. 314.
Some Aspects of Human Pharmacology of Tetraethylthiuramdisulphide (Antabus)-Alcohol Reactions. C. H. Hine, T. N. Burbridge, E. A. Macklin and others.—p. 317.
Reversal of Diurnal Variation in Renal Function in Cases of Cirrhosis with Ascites. R. A. Jones, G. O. McDonald and J. H. Last.—p. 326.
Studies in Glycine-2-C^{14} Metabolism in Man: II. Tissue Distribution. N. I. Berlin, B. M. Tolbert and C. Lotz.—p. 335.
Basal Secretion of Pepsin by Human Stomach. H. D. Janowitz and F. Hollander.—p 338.

Journal Lab. and Clinical Medicine, St. Louis

39:505-672 (April) 1952

Anemia of Renal Insufficiency as Induced by Bilateral Nephrectomy of Rabbit: With Emphasis on Its Hemolytic Nature. E. E. Muirhead, F. Jones and A. Grollman.—p. 505.
Diuresis Produced by Concentrated Dialyzed Human and Pregnant Mare Urine. Assay Procedure in Dog for Diuretic Substances. J. M. Little. —p. 518.
Effect of Repeated Phlebotomies in Hemochromatosis: Report of Three Cases. W. D. Davis Jr. and W. R. Arrowsmith.—p. 526.
Flocculation Tests; Contribution to Study of Their Mechanism. R. Armas-Cruz, G. Lobo-Parga and M. Madrid.—p. 533.
Serum Cholinesterase Activity in Liver Disease. J. D. Mann, W. I. Mandel, P. L. Eichman ond others.—p. 543.
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Transfusion of Human Blood Platelets with Note on Transfusion of Granulocytes. E. O. Hirsch and F. H. Gardner.—p. 556.
Effect of Cortisone and ACTH in Leukemia. W. S. Adams, W. N. Valentine, S. H. Bassett and J. S. Lawrence.—p. 570.
Determination of Packed Cell Volume. F. S. Schlenker and J. Noll. —p. 582.
Determination of Trapped Plasma in Centrifuged Erythrocyte Volume of Normal Human Blood with Radioiodinated (I^{131}) Human Serum Albumin and Radiosodium (Na^{24}). O. N. Vazquez, K. Newerly, R. S. Yalow and S. A. Berson.—p. 595.
*Effect of ACTH, Cortisone and Operative Stress upon Blood Cholesterol Levels. L. H. Kyle, W. C. Hess and W. P. Walsh.—p. 605.
Studies in Serum Proteins: VI. Extension of Standard Biuret Method to Estimation of Total Protein in Urine. P. W. Foster, J. J. Rick and W. Q. Wolfson.—p. 618.
Drainage of Radioactive Silver Colloids by Lymphatics Following Intrapulmonary Administration in Dogs. P. F. Hahn, G. Rouser, H. Brummitt and others.—p. 624.
Effects of Mixed Exchange Resins on Anionic and Cationic Metabolism. E. W. McChesney.—p. 629.
Cross-Resistance to Antibiotics: Effect of Repeated Exposures of Bacteria to Streptomycin or Neomycin on Resistance to Both of These and to Six Other Antibiotics. T. H. Haight, C. Wilcox and M. Finland. —p. 637.
Histochemistry of Lipid Carbonyl Compounds. G. Gomori.—p. 649.

Effect of Corticotropin, Cortisone, and Operative Stress on Blood Cholesterol.—Kyle and associates followed the blood cholesterol levels of patients during administration of corticotropin and cortisone and following the stress of surgical intervention, and compared the observed changes with variations seen in normal persons. They found that the determination of plasma cholesterol and cholesterol esters by chromatographic separation is reproducible within 2% on repeated determinations on the same sample. The variation in plasma cholesterol content on the same patient within two to eight hours is likewise within 2%, and for periods of from two to eight days the variation is approximately 5%. The administration of corticotropin in nine patients caused an average reduction of total cholesterol of 24%, and the greater decrease in cholesterol was well correlated with greater physiological stimulation by corticotropin. In two patients who obtained little stimulation from the corticotropin there was no significant depression of cholesterol. Intravenous administration of corticotropin to one patient for 20 days and to another for 14 days produced a marked decrease in plasma cholesterol. The effect of the administration of cortisone to nine patients was less consistent than that of corticotropin. The average change was a decrease of 7%, but a more marked decrease was observed in two patients who were given larger doses of cortisone. Compound F was given to one patient for 20 days, producing only a slight decrease in plasma cholesterol, although a marked decrease in the eosinophil count occurred. In 9 of 10 cases there was a decrease in plasma cholesterol following surgery, the decrease occurring later than the reduction in eosinophil count. It is suggested that the decrease in blood cholesterol that accompanies administration of corticotropin is caused by direct action of the adrenal hormone, either by inducing temporary impairment of hepatic function, or, more probably, by suppressing cholesterol synthesis.

Journal Nat. Cancer Inst., Washington, D. C.

12:701-936 (Feb.) 1952. **Partial Index**

Studies on Blood Supply of Tumors in Man: IV. Increased Oxygen Content of Venous Blood Draining Neoplasms. H. R. Bierman, K. H. Kelly and G. Singer.—p. 701.
Cytologic Study of Gastric Aspirate for Carcinoma Cells: Paraffin-Block Technic. A. Wollum, D. F. Glaser, H. C. Bryant and H. M. Pollard. —p. 715.
Action of Methylcholanthrene, Croton Oil, and 1,2-Benzanthracene in Induction of Skin Tumors in Strain DBA Mice. M. Klein.—p. 735.
Spontaneous Pulmonary Tumor in Rat: Report of Lesion. H. A. Horn and H. L. Stewart.—p. 743.
Factors Modifying Effect of X-Irradiation on Regression of Transplanted Lymphosarcoma. J. W. Hollcroft, E. Lorenz and M. Matthews. —p. 751.
Mortality of Mice After Total-Body Irradiation as Influenced by Alterations in Total Dose, Fractionation, and Periodicity of Treatment. H. S. Kaplan and M. B. Brown.—p. 765.
Acute Necrotizing Renal Papillitis Experimentally Produced in Rats Fed Mono-N-Methylaniline. J. White and P. Mori-Chavez.—p. 777.
Increase in Incidence of Leukemia in Hybrid Mice Bearing Thymic Transplants from High Leukemic Strain. L. W. Law.—p. 789.
Effect of Guanazolo on Antibody Formation. R. A. Malmgren, B. E. Bennison and T. W. McKinley.—p. 807.
Studies on Transmission of Mouse Mammary Tumor Agent by the Male Parent. O. Mühlbock.—p. 819.
Effect of Local Injections of Adrenalin on Epidermal Carcinogenesis in Mouse. A. C. Ritchie.—p. 839.
Effect of Arterial Occlusion on Epidermal Carcinogenesis in Rabbit. A. C. Ritchie.—p. 847.
Influence of Cortisone Acetate upon Growth of Transplanted Rhabdomyosarcoma in C3H Mice. G. M. Higgins and W. A. Bennett.—p. 851.
Ovarian Tumorigenesis Following Intrasplenic Transplantation of Ovaries from Weanling, Young Adult, and Senile Mice. M. Klein.—p. 877.
Proliferative Lesions Resembling Chordoma Following Puncture of Nucleus Pulposus in Rabbits. C. C. Congdon.—p. 893.
Acid and Alkaline Phosphatase of Serum and Hepatic Tissue of Rats Fed Carcinogens. A. S. Mulay and H. I. Firminger.—p. 917.
Metabolism of L-Histidine-2-C^{14} in Normal and Hepatoma-Bearing Rat. J. C. Reid, M. O. Landefeld and J. L. Simpson.—p. 929.

Journal of Nutrition, Philadelphia

46:141-270 (Feb.) 1952. **Partial Index**

Studies on Effects of Atabrine on Vitamin A Metabolism. K. Guggenheim. —p. 141.
Rancid Lard Effect on Rats Fed Complete and Riboflavin-Deficient Diets. H. Kaunitz, R. E. Johnson and C. A. Slanetz.—p. 151.
Study of Minimum Calcium Requirements of Adult Men. D. M. Hegsted, I. Moscoso and C. Collazos Ch.—p. 181.
Studies on Interrelationship Between Methionine and Vitamin B_6. H. J. DeBey, E. E. Snell and C. A. Baumann.—p. 203.
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Military Surgeon, Washington, D. C.

110:249-322 (April) 1952

*Clinical Aspects of Cold Injury. F. H. Mowrey and P. J. Farago.—p. 249.
Intramedullary Fixation of Fractures in Combat Casualties. E. A. Brav. —p. 254.
Modern Conception of Veterinary Public Health. J. H. Steele.—p. 258.
Military Government and Public Health. J. A. Tobey.—p. 260.
Public Health Aspects of Leptospirosis. W. S. Gochenour Jr.—p. 265.
Management in Army Hospitals. R. O. Pennepacker.—p. 269.
Treatment of Dislocated Condylar Fractures. E. G. Friedrich.—p. 271.
Procedures and Technique in Registrar Division of Veterans Administration Hospitals. J. M. DiPietro.—p. 273.
Epidemic Hemorrhagic Fever of Far East, or Endemic Hemorrhagic Nephroso-Nephritis: Short Outline of Disease, with Supplemental Data on Results of Experimental Inoculation of Human Volunteers. C. F. Mayer.—p. 276.

Clinical Aspects of Cold Injury.—Cold injury is trauma produced by exposure to cold, and includes such entities as chilblains, immersion foot, trench foot, and frostbite. Of 593 patients at the average age of 22, who with the troops in Korea had been exposed to temperatures of −20 to −30 F and were evacuated to the United States for frostbite treatment, 474 (80%) had either superficial or deep gangrene. Eighty per cent of the patients had involvement of the feet only, 16.8% had involvement of both feet and hands, and 3.2% had involvement of the hands only. Clinical experience with these patients showed that it is almost impossible to determine accurately the amount of tissue damage or whether amputation will be required without prolonged observation, up to three months in some cases. Conservative therapy is indicated to insure maximum preservation of function. The necrotic eschar on digits should be bivalved early to prevent contraction and further tissue damage. Ointments, particularly white petrolatum U. S. P. (vaseline®) gauze, are contraindicated as they result in ulceration and infection. Hexamethonium was the most effective vasodilator, as shown by high and prolonged elevation of skin temperature. This drug is just as effective as lumbar blocks and much simpler. Priscoline® (2-benzyl-4,5-imidazoline) hydrochloride administered orally was the next most effective agent. The use of vasodilators made no clinically evident difference in the rate of healing, but may have lessened the incidence of "post frostbite syndrome," such as cold feet with dependent rubor and/or cyanosis and hyperhidrosis. Administration of corticotropin (ACTH) and cortisone resulted in mild euphoria, lessening of pain, decrease in purulent drainage and odor, and apparently earlier demarcation of the necrotic area. Neither drug lessened the amount of tissue loss nor resulted in more rapid healing of the lesions. Soaks in warm, sterile, isotonic sodium chloride solution softened the eschar and in some cases apparently promoted more rapid healing.

New England Journal of Medicine, Boston

246:523-560 (April 3) 1952

*Use of Vaginal Smear as Screening Test. H. L. Lombard, M. Middleton, S. Warren and O. Gates.—p. 523.
Deep Venous Thrombosis in Leg Following Effort or Strain. C. Crane. —p. 529.
Allergy to Viral and Rickettsial Vaccines: III. Influence of Repeated Inoculations on Acquisition of Egg Allergy. B. Ratner, S. Untracht and F. Hertzmark.—p. 533.
Successful Treatment of Neuroblastoma: Report of Two Cases with Apparent Cures. H. W. Hudson Jr., J. W. Chamberlain and F. B. Becker.—p. 536.
Some Practical Aspects of Cancer Prevention. E. L. Wynder.—p. 538.

The Vaginal Smear as a Screening Test.—A single vaginal smear was obtained from each woman who attended the state-aided cancer clinics of Massachusetts between Jan. 1, 1945, and June 30, 1947. Three years after the original smear a follow-up history and, whenever possible, a pelvic examination and a repeat smear were secured. The total number of records was 3,581. Of the 210 women in whom cancer was diagnosed at the time of the original smear, 62.4% showed a positive test, 23.8% a questionable test, and 13.8% a negative test. Thus, the tests did not indicate that cancer was present in nearly one-seventh of those who had cancer of the uterus. Of 1,888 persons who had no apparent cancer of the uterus at the time of the smear or three years later, 1.9% originally showed a positive smear, 5.9% a questionable smear, and 93.1% a negative one. It is true that a few unsuspected cases of cancer have been discovered through the use of the vaginal smear, but the cost per discovered case was approximately $1,700. The large error found among the group most likely to have cancer (those who bleed) impairs the diagnostic value of this test for screening purposes. It does not seem feasible for a state health department to offer this test on an extensive scale for women without gynecologic symptoms, as the cost would be prohibitive and relatively few cancers would be found. The authors reiterate that they are not concerned with the value of the vaginal smear as a means of diagnosis per se, but rather with its use as a method of screening large populations. Its usefulness as a screening procedure is obviously less than in the study of an individual case.

New Jersey Medical Society Journal, Trenton

49:87-124 (March) 1952

The General Practitioner Treats the Uncomplicated Diabetic. E. O. Bauman.—p. 91.
Fate of Casein Hydrolysate Amino Acids Administered Intravenously to Human Subjects. R. N. Cagan, R. L. Klein and L. Loewe.—p. 99.
Hypoplastic Uterus in Infertility. M. Morgenstern.—p. 102.
Clinical Results with Prantal Methylsulfate: New Parasympathetic Blocking Agent: Preliminary Report. W. F. Vogel.—p. 105.

49:125-166 (April) 1952

The Cancer Program in New Jersey, Part VI: Administration of Radio-Active Isotope Program in New Jersey. W. O. Wuester, W. E. Bray, J. S. Gallo and others.—p. 129.
Functional Disease of Colon: Roentgen Study Based on 200 Cases. R. J. Gross, O. H. Cohen and C. R. Weinberg.—p. 131.
Teen-Age Narcotic Problem in New Jersey. E. P. Ivey and J. L. Evans Jr.—p. 136.
Trichlorethylene in Obstetrical Anesthesia. M. Fenster and H. Levy. —p. 138.
Clinical Diagnosis and Case Management. G. V. Stoddard.—p. 139.
Acute Methemoglobinemia Due to Aniline: Report of Case. A. D. Casciano.—p. 141.
Rehabilitation of Aged Chronic Invalid. J. O. Smigel.—p. 143.
Brain Anoxia: Report of Case. F. Frisch.—p. 146.
Method of Psychotherapy for General Practitioner. J. Chernus.—p. 148.
Scabies Epidemic in an Institution. H. C. Goldberg.—p. 152.

Western J. Surg., Obst. & Gynecology, Portland, Ore.

60:93-140 (March) 1952

Simplified Putti-Platt Reconstruction for Recurrent Shoulder Dislocation: Preliminary Report. E. A. Brav and V. H. Jeffress.—p. 93.
Diabetes and Pregnancy. J. M. Whitely and T. W. Adams.—p. 98.
Neurilemoma Involving Main Peripheral Nerve Trunk with Complete Excision and Preservation of Nerve Continuity and Function: Report of Three Cases. J. P. Trommald.—p. 108.
Some Considerations Regarding Use of Vascular Grafts. L. R. Sauvage and H. N. Harkins.—p. 113.
Vaginismus as Cause of Dyspareunia: Report of Cases and Method of Treatment. S. P. Hall.—p. 117.
Anal Ileostomy in Chronic Ulcerative Colitis. W. B. Hutchinson.—p. 121.
*The Pancreas and the Steering Wheel. M. Joseph.—p. 129.
Carcinoma of Cervix Complicating Pregnancy. A. P. Hudgins.—p. 132.

Injuries to the Pancreas by Steering Wheels.—Having observed three cases of subcutaneous nonpenetrating trauma to the pancreas within a period of a few months, the author suggests that pancreatic trauma is not as rare as is generally believed, and therefore the notion that the pancreas is invulnerable because of its cushion protection by the stomach and transverse colon should be discarded. When a ruptured viscus is suspected after severe abdominal trauma, and no injury of the liver, spleen, or the hollow viscera is found, the pancreas should always be carefully examined. Serum amylase and lipase should be determined in all cases of vague epigastric symptoms in which results of careful routine tests, including x-ray examination, are negative. Surgery should be directed toward the control of hemorrhage, relief of excessive tension in the capsule of the pancreas, and removal of septic material and fluid. The value of drainage is uncertain. All three patients had had automobile accidents in which the steering wheel had been forced against the abdomen and chest. The possibility of a pancreatic trauma should be considered whenever a blow to the upper abdomen has been sustained. Early exploration and repair of damage are important.

FOREIGN

Acta Paediatrica, Stockholm

41:101-206 (March) 1952. **Partial Index**

*Simultaneous Visualization of Posterior and Anterior Mediastinum After Insufflation in Peridural Space: Tridimensional Tomographic Study. G. Sansone and A. De Maestri.—p. 101.
Weight of Thyroid Gland in Infants up to 2 Years of Age. H. Tähkä. —p. 108.
Airborne Infections: VI. Continued Investigations into Control of Dust-Borne Streptococcal Infections in Infants' Wards. G. Laurell.—p. 124.
Iron Metabolism in Infants: I. Intake of Iron in Breast Feeding and Artificial Feeding (Milk and Milk Foods). Y. M. Feuillen and M. Plumier.—p. 138.
ACTH in Treatment of Juvenile Rheumatoid Arthritis. J. Vesterdal, O. Remvig and M. Sprechler.—p. 145.
Report of Two Cases of Acrodynia Appearing After Calomel Therapy but Without Excretion of Mercury in Urine and Cured with Dimercaprol (BAL). R. Houet.—p. 158.
Lipochondrodystrophy with Cutaneous Deposits. B. Andersson and O. Tandberg.—p. 162.
Sexual Precocity in Male Infant Due to Estrogenic Ointment. L. Hesselvik.—p. 177.

Visualization of Mediastinum.—Study of the posterior mediastinum is difficult, particularly in children, in whom gas insufflation following transtracheal puncture has been considered inadvisable. The authors found the intraspinal, extradural approach, that is, injection of a gas contrast medium into the peridural space, ideal for use in children. This technique permits simultaneous, sharp visualization of both the anterior and posterior mediastinum. It is easy, safe, and well tolerated by children. Used with tomography (in anteroposterior, lateral, and axial transversal projections) this method gives interesting tridimensional pictures.

British Journal of Dermatology, London

64:129-168 (April) 1952

Bloch-Sulzberger Syndrome (Incontinentia Pigmenti). H. Haber.—p. 129.
Pathogenesis of Incontinentia Pigmenti. With Observations on Associated Eye Disturbance Resembling Retrolental Fibroplasia. G. H. Findlay. —p. 141.
Vascular Naevi and Their Treatment. R. T. Brain and C. D. Calnan. —p. 147.

British Medical Journal, London

1:831-880 (April 19) 1952

Fifth and Seventh Cranial Nerves in Relation to Nervous Mechanism of Taste Sensation: New Approach. W. Harris.—p. 831.
*Mass B.C.G. Vaccination in Malta: Report on B.C.G. Vaccination Campaign Held by I.T.C. in Malta in 1950. V. Zammit-Tabona. —p. 837.
Gall-Stones: Clinical Survey. T. R. Littler and G. R. Ellis.—p. 842.
Pulmonary Tuberculosis and Pregnancy. J. R. Edge.—p. 845.
Value of Pneumoencephalography in Diagnosis of Fits. J. Marshall and C. W. M. Whitty.—p. 847.
Isolated Neuritis of Anterior Interosseous Nerve. L. G. Kiloh and S. Nevin.—p. 850.
Verbal Usage of the CDE Notation for Rh Blood Groups. S. Haberman and J. M. Hill.—p. 851.
Response of Megaloblastic Anaemias of Pregnancy to Animal Protein Factor: Preliminary Report. H. Foy, A. Kondi and A. Hargreaves. —p. 852.

Mass BCG Vaccination in Malta.—Between March and June, 1950, 54,328 persons in Malta were tuberculin-tested, and 38,681 were vaccinated with BCG. Of the latter 36,320 were between the ages of 1 and 18 years and 2,361 were over 18. This campaign was held because destruction of habitable dwellings during World War II and the ensuing housing shortage had resulted in severe overcrowding, favoring spread of tuberculosis. The tuberculin tests indicated that between the ages of 16 and 20 more boys than girls were infected with tubercle bacilli. This is in accord with the finding that in this age group more males developed pulmonary tuberculosis, in whom, however, it was less likely to be fatal than in females. The incidence of tuberculosis infection and of pulmonary tuberculosis were lower in the rural areas, while in the semirural, suburban, and urban areas they were approximately the same. BCG vaccination was carried out by means of Wallgren's intradermal injection technique, using 0.1 ml. of a vaccine containing 0.025 mg. of BCG or about 1 million "BCG bacilli" per 0.1 ml. An accelerated reaction at the site of inoculation was observed in 11 persons. Between the 30th and 53d days after vaccination 23 patients had discharging ulcers, which tended to heal rapidly. Of 54 persons with lymph node enlargement in the axilla following BCG vaccination, 2 had a secondarily infected BCG ulcer, and 2 complained of discomfort on movement, while in 21 children between the ages of 1 and 6 years the condition progressed to suppuration. Elevation of temperature following the vaccination was rare, one person had erythema nodosum, and 17 had phlyctenular conjunctivitis. To check the efficacy of both the vaccine and the technique of its administration, postvaccination tuberculin tests were given to 2,421 unselected persons according to the epinephrine-Pirquet technique. Positive reactions occurred in 98.95% of these persons. Up to 12 to 15 months after the campaign no cases of tuberculosis had been reported among persons vaccinated with BCG.

Edinburgh Medical Journal

59:161-212 (April) 1952

*BCG-Vaccination as Public Health Measure. A. Wallgren.—p. 161.
Determination of Bacterial Sensitivity to Antibiotics. J. C. Gould and J. H. Bowie.—p. 178.
Staph. Aureus Air Infection in Maternity Hospital. A. T. Wallace and J. P. Duguid.—p. 200.

BCG Vaccination as Public Health Measure.—Experience with BCG vaccination in about 17,000,000 persons in the Scandinavian countries, in the war-devastated countries in Europe, and in undeveloped countries outside Europe suggests that adequately performed BCG vaccination produces specific immunity strong enough to provide protection to a great extent against severe tuberculosis, miliary tuberculosis, and tuberculosis meningitis, and to a certain extent against pleurisy and postprimary pulmonary tuberculosis. The morbidity and mortality rates of tuberculosis have been reported to be lower in groups of adequately vaccinated persons than in nonvaccinated groups of tuberculin-negative persons. Most observers believe that BCG vaccination should be accepted as a public health measure against tuberculosis. BCG vaccination in itself will not abolish tuberculosis in a community. Other measures are more important, such as those aimed at preventing tuberculous infection, at increasing the natural resistance of the population by a high standard of living, at early detection of tuberculous disease, and at giving every person in need of it adequate treatment. The object of BCG vaccination is to produce artificial specific immunity in persons who still are uninfected, and the earlier artificial immunity is established the better. In a country with high incidence of tuberculosis vaccination of children as young as possible is advisable as a public health measure. If most babies are born in maternity hospitals, the BCG vaccination is most conveniently performed on newborn infants, without any preliminary tuberculin testing. By tuberculin control and revaccination if necessary, the virulent infection, when and if it occurs, is generally prevented from producing clinical primary tuberculosis and early postprimary disease. In persons of all age groups exposed to sources of infection, such as children in homes with tuberculous patients and hospital personnel, BCG vaccination should as a public health measure be performed in those still tuberculin-negative.

J. of Canadian Association of Radiologists, Montreal

3:1-30 (March) 1952

Physical Characteristics of Radiation in Cobalt^{60} Beam Therapy. H. E. Johns.—p. 2.
Clinical Possibilities of Cobalt^{60} Beam Unit. T. A. Watson.—p. 7.
Room Protection Measurements for Cobalt^{60} Teletherapy Units. W. R. Dixon, C. Garrett and A. Morrison.—p. 11.
Cobalt^{60} Beam Therapy: Some Influences and Advantages. I. H. Smith. —p. 16.
Considerations in Design of Cobalt^{60} Beam Therapy Equipmnt. D. T. Green and R. F. Errington.—p. 20.
*Betatron in Cancer Therapy: Part II. T. A. Watson and C. C. Burkell. —p. 25.

Betatron in Cancer Therapy.—Observations on 58 patients with advanced cancer treated by means of a 22 mev betatron are reviewed. A 22 mev betatron has limited usefulness in treatment of deep-seated lesions. It does not appear to have specific bi-

ological advantage over conventional x-rays, but does have certain physical attributes that can be used to advantage. Constitutional effects are minimal. Lack of variation of depth dose with field size makes for simplicity. The low skin dose compared with a very high depth dose is of great value. The immediate results, in advanced cases of cancer of the cervix and bladder, were promising, but the doses given apparently caused disappearance of detectable signs of the tumor rather than eradication. It has been impossible to achieve a dose lethal for the tumor in most cases. The limiting factor in treatment of cancer of the cervix is the effect on the bowel and bladder, but even irradiation to the pelvis is possible. A dose of 6,000 r to the whole pelvis delivered in three weeks was considered the maximum possible. Considerable palliation was achieved in advanced tumors of the lung and brain. The response of cancer of the rectum was disappointing.

Lancet, London

1:775-830 (April 19) 1952

Medical Research Council National Tuberculin Survey 1949-50: Background and Methods of Survey. R. T. James, E. C. H. Huddy, J. E. Geddes and others.—p. 775.
*Thymectomy in Treatment of Myasthenia Gravis. R. T. Ross.—p. 785.
Review of 200 Chronic Alcoholics. L. Williams.—p. 787.
Assay of A.C.T.H. on Thymus of Nestling Rat. H. M. Bruce, A. S. Parkes and W. L. M. Perry.—p. 790.
*Prevention of Acute Dinitro-Ortho-Cresol (D.N.O.C.) Poisoning. P. L. Bidstrup, J. A. L. Bonnell and D. G. Harvey.—p. 794.
Estimation of Dinitro-Ortho-Cresol in Blood. D. G. Harvey.—p. 796.
Diabetic Acidosis Without Ketonuria. J. Henneman.—p. 797.
Extensive Resection of Small Bowel. J. H. Johnston.—p. 799.

Thymectomy in Myasthenia Gravis.—A benign hyperplastic thymus gland was removed from 100 consecutive patients with myasthenia gravis. Only one of the seven patients who died postoperatively died of myasthenia gravis. Of the survivors, 41 patients have no symptoms and require no treatment; 26 have slight and inconstant symptoms and are able to work with no limitations due to myasthenia gravis, with irregular and much less treatment than before the operation; 20 patients have fewer or less severe signs and symptoms, and respond to a significantly smaller dose of neostigmine as well or better than before the operation; and 6 patients are unchanged or worse. The benefit was greatest in the patients who had had myasthenia for the shortest time before operation. The age of onset did not seem to be significant. Comparison with three series of patients treated by medical means alone reveals that among these the proportion of cured or greatly improved is smaller and the proportion of deaths due to myasthenia gravis much higher than in the group presented here.

Prevention of Acute Dinitro-Ortho-Cresol Poisoning.—In Great Britain eight fatal cases of poisoning have occurred since 1945 in men engaged in the manufacture of dinitro-ortho-cresol, and in spray operators using dinitro-ortho-cresol for control of weeds in cereal crops. No cases of poisoning have been recorded among men who use the substance as a late winter wash on fruit trees. Experiments on volunteers showed that, when the dinitro-ortho-cresol level in the blood was about 20 μg per gram a further dose of about 1 mg. per kilogram of body weight led to a sharp increase in the concentration of this compound in the blood, and when this was more than 40 μg per gram all the volunteers had headache, lassitude, and general malaise. When the level of this substance in the blood was about 20 μg, all the volunteers had an exaggerated feeling of well-being. Single estimations were made on blood collected from 23 workers engaged in manufacture of dinitro-ortho-cresol, 39 men using dinitro-ortho-cresol as a late winter wash on fruit trees, and 133 spray operators applying dinitro-ortho-cresol to cereal crops. The dinitro-ortho-cresol levels in four cases of acute poisoning show the correlation between the blood level and the symptoms and signs of poisoning. A man should be removed from further contact with this compound for a minimum of six weeks if the dinitro-ortho-cresol level eight hours after the last exposure is 20 μg per gram or higher. Since the main route of absorption is by inhalation, respirators should be worn, especially by spray operators. The authors consider that estimation of dinitro-ortho-cresol levels in the blood might prove a valuable measure in the prevention of acute poisoning, but that determination of dinitro-ortho-cresol in the urine is unlikely to prove a reliable test.

Medical Journal of Australia, Sydney

1:385-424 (March 22) 1952

*Surgical Relief of Mitral Stenosis: Preliminary Report. F. H. Mills, J. K. Maddox, R. B. Blacket and A. J. Palmer.—p. 385.
Toxoplasmosis: Review of Literature and Report of Case. I. B. Jack.—p. 391.
Laryngeal Ventricle and Its Appendix (Laryngeal Saccule) and Their Associated Pathological Lesions, with Report of Three Cases of Laryngocele. G. Swinburne.—p. 396.
Secretion of 3,3'-Ethylidene Bis (4-Hydroxycoumarin) in Milk. P. Fantl and J. F. Nelson.—p. 404.
Renal Trauma. A. Gee.—p. 405.
The Q-T Interval of Electrocardiogram in Elderly Subjects. P. Hagen.—p. 407.
Flexible Plastic Tube Adapter for High-Pressure Injections. D. G. Renton.—p. 408.

Surgical Relief of Mitral Stenosis.—Commissurotomy according to the techniques of Bailey and Brock was performed by a posterolateral approach through the bed of the left fifth rib in 23 selected patients with mitral stenosis. The first patient was treated in March, 1951. Separation of the valve cusps at the commissures with the finger was attempted. If this was not possible, the finger was withdrawn and a small commissurotomy knife fashioned to fit the curve of the finger was inserted. With the knife it was usually easy to slit the valve and then carry out digital dilatation to the muscular wall of the heart. One patient with severe stenosis died during the induction of anesthesia, although adequately prepared for surgical intervention, and a second patient with auricular fibrillation of several years' standing died of embolism in the cerebral and iliac vessels on the third postoperative day. Patients with a very large heart, with established right-sided failure, with free mitral regurgitation, with significant aortic valve disease, or with active rheumatic carditis should not be operated on. In patients between 30 and 45 years of age who are not in a state of congestive failure, who have not had severe congestion, but who have had recurrent "bronchitis," pulmonary edema or hemoptysis and are seriously incapacitated, the operative mortality should be negligible and the results should be good. Two of the 21 living patients were not yet well enough for their improvement to be assessed, but 14 showed great improvement, 2 were only slightly improved, and 3, in whom for technical reasons dilatation was unsuccessful, were unimproved. The only serious postoperative complication was auricular fibrillation, which was controlled with digitalis and quinidine. The severity of the lesion was demonstrated preoperatively by cardiac catheterization in four of the first six patients operated on; the authors now carry out this procedure as a routine measure before considering surgical treatment. The authors' results and those of other workers suggest that sooner or later every patient with mitral stenosis should be treated surgically.

Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

96:661-722 (March 22) 1952. **Partial Index**

Periarteritis Nodosa Cured with Corticotropin. A. J. M. Lohman.—p. 671.
Combat of Bovine Tuberculosis and Change in Epidemiologic Picture of Tuberculosis. A. C. Ruys.—p. 676.
New Methods for Concentration of Ameba Cysts in Feces. J. J. Laarman.—p. 681.
*Persistent Excretion of Tubercle Bacilli by Patients with Clinically Inactive Pulmonary Lesions. C. Dijkstra.—p. 690.

Excretion of Tubercle Bacilli by Patients with Inactive Pulmonary Lesions.—Frequent control tests were carried out over long periods on the sputum and gastric contents of 445 patients who had had an open form of pulmonary tuberculosis but had been clinically cured. It was found that 18% continued to eliminate tubercle bacilli intermittently. In about 15% of the patients the last 10 specimens examined for tubercle bacilli were negative, but since prolonged intermission in excretion of bacilli of from four to six months had occurred before, it is not certain whether the lesions in these patients are definitely closed.

Presse Médicale, Paris

60:489-508 (April 5) 1952. **Partial Index**

Importance of Auscultation of Thyroid in Diagnosis of Basedow's Disease. C. Lian.—p. 489.
*Anti-Edematous Therapy Combined with Palliative Chemotherapy of Epithelial Cancers. A. Morel and A. Josserand.—p. 490.
Pathology and Treatment of Abortions of Endocrine Origin. M.-F. Jayle. —p. 492.

Anti-Edema Therapy in Epithelial Cancers.—The frequent early, severe relapses following incomplete cytocidal therapy in cancer may result from perifocal swellings caused by an allergic reaction to the products of partial tumor lysis. Neoplastic cells proliferate in the edematous fluid and the exudates, carried by greatly dilated lymphatic vessels, cause distant, so-called inflammatory, adenopathies; these in turn are colonized by the cancer cells. Excellent palliative results with apparent stabilization of the tumors have been obtained by treatment in three stages: a cytocidal attack; brief, intense therapy to reduce edema; and a fairly long period of antihistaminic therapy designed to prevent reinfiltration of the perifocal area. Treatment begins with the intravenous administration of sodium oxyferriscorbone in 2 or 3 cc. of 30% hypertonic glucose solution morning and evening for five days to prepare the perifocal area for the cytocidal attack. No treatment is given on the sixth day, but on the seventh colchicine is given intravenously followed by from four to six additional injections of sodium oxyferriscorbone. Twenty days of antihistaminic therapy follow, including intradermal injection of an antihistamine solution every other day, to prevent the reappearance of edema. The complete series is then repeated as often as necessary. The treatment is generally well tolerated and may be individualized by such means as altering the dose or using other cytocidal preparations alternately with colchicine. The pain of epithelial cancer, which is usually caused by pressure of the fine nerve fibers owing to perineoplastic cellulitis, diminishes or disappears entirely after reduction of edema, and the effect of the cancerocidal substances is prolonged and accentuated by the decongestive treatment.

Riforma Medica, Naples

66:197-224 (Feb. 23) 1952

*Q Fever in Umbria Region: Clinical Observations in 51 Cases. R. Frascarelli.—p. 197.
Anti-Allergy Treatment in Severe Shock Caused by Burns. A. Loizzi. —p. 202.
Danger and Harm of Treating Ureteral Lithiasis with Oligo-Mineral Waters. M. Sorrentino.—p. 205.
Use of Bogomoletz Serum. G. Carnera.—p. 207.

Q Fever in Umbria Region.—The occurrence of Q fever is reported in 51 persons from the Umbria region. The incubation periods ranged from 14 days to 26 days. The symptoms were elevation of temperature, severe headaches, profuse sweating, asthenia, and pulmonary involvement. Laboratory tests revealed an increased erythrocyte sedimentation rate during the acute stage of the disease, slight but frequent albuminuria, and in seven patients decreased reaction to tuberculin. The blood picture and the differential blood count remained unchanged. The liver was enlarged in four patients only, of whom two were alcoholics and one both alcoholic and diabetic. Since the urine urobilin level was normal, there was no bilirubin in the blood, and the Takata-Ara test was normal, the author concludes that usually Rickettsia burneti cause slight liver damage. Repeated tests demonstrated that the complement fixation was always positive and that the complement-fixing antibodies had not been influenced by antibiotic treatment and were still in circulation several months later. All these patients, except one, had a bronchopneumonic process, but in none was Q fever associated with another disease. According to the author, Q fever occurs both with and without pulmonary involvement. Diagnosis based on clinical findings is inadequate and laboratory tests for Rickettsia burneti are the decisive factor in differential diagnosis from primary atypical pneumonia and other febrile processes. Treatment of Q fever is not difficult, since the disease may regress spontaneously. Fifteen patients were treated with aureomycin, 13 with terramycin, 7 with chloramphenicol (chloromycetin®), and 1 with paraaminobenzoic acid. Aureomycin and terramycin were equally effective, while chloramphenicol failed in two patients. In all the other patients the disease disappeared spontaneously, suggesting that the effects of antibiotics on Q fever should not be overemphasized.

Schweizerische medizinische Wochenschrift, Basal

82:372-440 (April 12) 1952. **Partial Index**

Incidence of Sensitization by Mercury as Cause of Infantile Acrodynia. T. Baumann.—p. 375.
Accidental Death in Childhood, Particularly in Motorized Street Traffic. J. Dettling.—p. 377.
*Etiology of Retrolental Fibroplasia. H. Goldmann and W. Tobler. —p. 381.
Role of Infection in Development of Atrophic Conditions in Infants. P. Kiss.—p. 387.
Localization of Lobar Pneumonia in Childhood. S. Engel.—p. 403.
Examination of Functional Capacity of Adrenal Cortex in Early Childhood. E. Rominger.—p. 411.
*Treatment of Celiac Disease with Corticotropin and Cortisone. J. Ugland, L. Wennevold and L. Salomonsen.—p. 420.

Etiology of Retrolental Fibroplasia.—A single case of retrolental fibroplasia was discovered among 570 prematurely born infants who weighed less than 2,000 gm. at birth. A search for etiological factors revealed that the recent introduction of a new type of incubator and the use of high concentrations of oxygen probably played a part in development of retrolental fibroplasia. They suggest two possible causes: (1) the unphysiological administration of oxygen may cause the eye lesions or (2) although the prematurely born infant may become adapted to the oversupply of oxygen, damage occurs when the baby is removed from the high oxygen atmosphere. The authors feel that oxygen must be used cautiously in prematurely born infants.

Corticotropin and Cortisone in Celiac Disease.—The four children with celiac disease whose cases are reported in this paper were boys between 15 months and 5½ years of age. They had had symptoms of celiac disease for from six months to three years. The response to dietetic treatment had been unsatisfactory. Treatment with corticotropin and cortisone was continued for from four to seven weeks, during which a modified dietetic treatment was continued. Corticotropin was given for two days in large doses, then for several weeks in an adjusted maintenance dose and finally in slowly decreasing doses. Patients who were treated with cortisone were given some corticotropin at the end of the course of cortisone. Treatment with corticotropin or cortisone effected improvement in the general condition, mood, appetite, appearance and fat content of stools, sideropenia, anemia, hypoproteinemia, and the blood sugar tolerance tests, but no effect was noted on osteoporosis, on the retarded development of the epiphyseal nucleus, or on the roentgenologically demonstrable changes in the small intestine.

Semaine des Hôpitaux de Paris

28:1085-1118 (April 6) 1952

Cortisone in Cirrhosis of Liver in Alcoholics. R. Cachera and F. Darnis. —p. 1085.
*Biochemical Diagnosis of Renal Lithiasis. J. Cottet.—p. 1096.

Biochemical Diagnosis of Renal Lithiasis.—Since dietetic and medicinal treatment of renal lithiasis varies according to the chemical nature of the lithiasis, biochemical diagnosis of the lithiasis was attempted by the author on the basis of a test in which crystalluria is induced. The crystalline sediment and the pH were studied systematically in the urine specimens collected in the course of one day while the specific gravity of these specimens varied physiologically. For the induced crystalluria test to be of any value, the specific gravity must exceed 1.015 in at least two or three specimens of the urine. The test was performed on 24 persons who had no signs of renal lithiasis, on 18 patients with renal colic but without evidence of calculi, and on 56 patients who had urinary calculi. Results of the tests suggested that it may be possible to infer the chemical nature of the lithiasis from the constitution of the urinary crystalline sediment. This concept was confirmed by a comparative study of the results of the induced crystalluria tests, which were done in 28 patients with one or several urinary calculi, the chemical constitution of which was known. The presence of a urate sediment indicates the formation of calculi of uric acid or oxalic

acid. The presence of an oxalate sediment does not provide precise indications but is suggestive of the formation of calcium oxalate or phosphate calculi. The presence of uric acid in a mixed sediment rules out phosphate lithiasis, and the presence of phosphates in a mixed sediment rules out uric acid lithiasis.

Strahlentherapie, Munich

86:489-640 (No. 4) 1952. **Partial Index**

Results of Irradiation Therapy of Carcinoma of Cervix at the University Women's Clinic in Munich. H. Eymer and J. Ries.—p. 535.
Treatment of Malignant Melanoma. W. Hellriegel.—p. 548.
Myasthenia Gravis Pseudoparalytica as Disturbance of the Sympathetic System and Its Modification with the Aid of Functional Irradiation Therapy. J. Trautmann and J. G. Frey.—p. 571.
New Experimental Results with Thorium X on Human Tissues: Diagnosis by Means of Radioactive Isotopes. H. Moser and E. Schoen.—p. 539.
*Spontaneous Fractures After Roentgen Irradiation. W. Greve.—p. 617.

Spontaneous Fractures After Roentgen Irradiation.—Most reports of spontaneous fractures following roentgen irradiation concerned the neck of the femur. This paper reports one case of bilateral fracture of the neck of the femur in a man, aged 79, in whom 5,500 r had been applied to a tumor of the penis and prophylactic doses of 1,800 r to each inguinal field. The fractures of the neck of the femur were accompanied by bone atrophy, but there were no signs of bone metastases. Whereas the bone tolerance dose is usually estimated at between 3,800 and 4,300 r, in this patient it was estimated that the neck of the femur had received a focal dose of only about 1,500 r. In the three other cases reported in this paper, rib fractures followed intensive postoperative irradiation after mastectomy for cancer. There was no callus formation in these cases; on the contrary, the irregular fracture cleft became enlarged, in some cases up to 3 cm., owing to partial decomposition of the bone. Simultaneously, fibrosis of the corresponding lung field developed in these cases. In these patients with spontaneous rib fractures the bone tolerance dose had been exceeded.

Tubercle London

33:97-130 (April) 1952. **Partial Index**

Home Treatment of Respiratory Tuberculosis. H. Stevens.—p. 107.
Some Aspects of Composite Area Surveys in Mass Radiography. E. Psoner.—p. 112.
Effect of Penicillin on Mycobacteria in Vitro and in Vivo. M. A. Soltys.—p. 120.

West African Medical Journal, Nigeria

1:1-42 (Jan.-Feb.-March) 1952. **Partial Index**

Recent Advances in Tropical Medicine. Blackwater Fever in West Africa. B. Maegraith.—p. 4.
Clinical Picture and Treatment of Whipworm Infection. R. C. Jung and D. B. Jelliffe.—p. 11.
Oedematous Beri-Beri in Gambian Palm Wine Tappers. J. H. Walter and D. A. Smith.—p. 21.
*Cerebral Thrombosis in Sickle Cell Anaemia. D. B. Jelliffe.—p. 38.

Cerebral Thrombosis in Sickle Cell Anemia.—Sickle cell anemia is characterized by a chronic or recurrent hemolytic process and a tendency toward formation of intravascular thromboses. American authors who reported the occurrence of cerebral thrombosis in sickle cell anemia concluded that almost any neurological syndrome may be produced, including coma, hemiplegia, aphasia, and cranial nerve lesions, and they emphasized the importance of examining the blood for sickling in all cases of neurological disease in Negro patients. In this paper Jelliffe describes a girl, aged 4, who had shown signs of general ill health and had become drowsy the day before hospitalization. Despite intramuscular treatment with quinine and procaine penicillin, the child rapidly became more comatose and died. A diagnosis of sickle cell anemia was made, in view of the blood count, slight icterus, rapid development of in vitro sickling, and the presence of in vivo sickling. An associated intracerebral thrombosis suggested by the patient's condition was confirmed at autopsy. Clubbing of the fingers and toes and parietal bossing of the skull have been described as occurring in sickle cell anemia. The radiological appearance of the bosses reveals a characteristic perpendicular spiculated arrangement. The sickle cells seen in this case tended to have a long filamentous shape. This is in agreement with the findings of Foy, Kondi and Brass, who feel that this type of sickle cell occurs only in cases of sickle cell anemia, in contrast to the more compact, regular, half-moon cells seen in carriers of the sickle cell trait. This observation, which requires confirmation, would provide a rapid method of differentiating the two manifestations of sickle cell disease.

Ztschr. f. Hygiene & Infektionskrankh., Heidelberg

134:123-218 (No. 2) 1952. **Partial Index**

Further Tests on Sterility and Stability of Vaccine Lymph Prepared with Streptomycin. A. Herrlich and M. Bednara.—p. 123.
*Pylorospasm: Prophylaxis, Pathogenesis, and Therapy. G. Jordan.—p. 129.
Antibiotics of Animal Origin. M. Pavan.—p. 136.
Action of Cobalt on Antibody Titer of Blood: Experiments on Rabbits. G. Gillissen.—p. 173.
Coxsackie Viruses: With Consideration of Their Relationship to Virus of Poliomyelitis. F. H. Top.—p. 183.
New Neurotropic Viruses Found in Africa. K. C. Smithburn.—p. 212.

Pylorospasm.—The literature on pylorospasm reveals that it occurs almost exclusively in northern latitudes, 10 to 15 times more frequently in boys than in girls, and oftener in breast-fed infants. These and other aspects suggest a spastic genesis produced by insufficient calcium ions, which results in a tendency for tetany to develop. It has been observed that shortly after delivery the calcium content of the serum of many infants is decreased, presumably as the result of deficiency of vitamin D in mother and child. The sex ratio of pylorospasm is similar to that of rickets. Inter-relations between vitamin D and hypophyseal, gonadal, and adrenal hormones also point to disturbances in the calcium metabolism: the parathyroids are larger in females than in males, and the sex hormones influence calcium metabolism. Pylorospasm occurs most frequently during the third week of life when the serum calcium content is the lowest. Pylorospasm is thought to be the result of latent tetany in which vitamin D deficiency, nutritional and endocrine factors are involved. This concept of pylorospasm implies that calcium and vitamin D should be given prophylactically to the expectant mother, particularly near delivery. During the first four weeks the infant should be nursed often, but the amounts given at each feeding should be small. Blood for transfusions should contain heparin but should never be citrated. Infusion of Tyrode's solution and calcium intravenously is recommended. Acid therapy in the form of ammonium chloride and calcium chloride should be accompanied by control of the alkali reserve. If medical therapy fails, surgical treatment in the form of Ramstedt's operation should be resorted to.

Zeitschrift für Urologie, Leipzig

45:193-256 (No. 4) 1952. **Partial Index**

Embryonal Mixed Tumors of Kidney in Adults. H. G. Gleichmann.—p. 193.
Stones in Diverticuli of Bladder. L. Pfau.—p. 206.
Problem of Primary Cortical Focus in Renal Tuberculosis. H. Eufinger.—p. 213.
Recanalization of Mechanically Closed Ureters. W. Dornes, H. Lurz and B. Sachsse.—p. 229.
*Rare Metastases of Prostatic Carcinoma in Testis, Epididymis and Spermatic Cord. S. Rummelhardt.—p. 231.

Metastases of Carcinoma of Prostate in Testes, Epididymis, and Spermatic Cord.—Reports of metastases of the prostatic carcinoma to the testes have been rare. Four such cases have been reported in the American literature, and Eufinger describes an additional case. In all of these cases the metastasis was discovered during microscopic study of the surgical specimen. Later, in the course of 14 orchidectomies a change indicative of chronic inflammation was observed in one epididymis of one patient and the testis was removed on this side. Microscopic examination of the surgical specimen revealed cancerous infiltration in the spermatic cord and in the epididymis. Such mestatization from the prostate to spermatic cord, epididymis, and testis may take place by the blood or lymph streams or by canaliculi. When orchiectomy is done, the epididymis and spermatic cord should be carefully examined, so that easily removed metastases will not be left behind. Since the testicular metastases were observed neither clinically nor during operation, microscopic examination of the testicular parenchyma should not be neglected.

BOOK REVIEWS

The Prevention of Rheumatic Fever. By Lowell A. Rantz, M.D., Associate Professor of Medicine, Stanford University School of Medicine, San Francisco. Publication number 125, American Lecture Series, monograph in American Lectures in Circulation, edited by Irvine H. Page, M.D., and A. C. Corcoran, M.D. Cloth. $2.25. Pp. 66, with 1 illustration. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, 1952.

This brief monograph attempts to bring together the information that has accumulated in recent years regarding the role of Streptococcus in rheumatic fever. The author is primarily concerned with presenting evidence indicating the importance of prevention and early treatment of infection by the Streptococcus in the prophylaxis of rheumatic fever. On the basis of such evidence, specific recommendations for the prevention of rheumatic fever are discussed.

This monograph should be of great value to the pediatrician and internist interested in the problems of rheumatic fever. The brevity and simplicity of presentation should increase its usefulness for the student and house officer. With the exception of the small number of persons who still question the role of Streptococcus in rheumatic fever, there is little in the main theme of the subject matter that is controversial. Questions might be raised concerning the specific prophylactic procedures recommended, although most of them seem reasonable; however, the validity of the repeated injunctions against the use of sulfonamides in active rheumatic fever may be doubted. There seems to be no objective data to support this view, although it has been widely accepted by clinicians. This book may not be regarded as a definitive work in the general field of rheumatic fever, and its conclusions may require revision with increasing knowledge; nevertheless, it should serve as a valuable progress report on the present state of knowledge with respect to the control of rheumatic fever.

Case Histories in Psychosomatic Medicine. By Staff of Psychiatric Service, Massachusetts General Hospital, Boston. Edited by Henry H. W. Miles, M.D., Stanley Cobb, M.D. and Harley C. Shands, M.D. Cloth. $4.50. Pp. 306, with 4 illustrations. W. W. Norton & Company, Inc., 101 Fifth Ave., New York 3, 1952.

Selected cases from the clinical conferences conducted by the Psychiatric Service of the Massachusetts General Hospital are discussed from the point of view of this group's experience and approach to the understanding and handling of psychosomatic problems. Emphasis is on expanding psychiatric education, and the necessity of "team work" of psychiatrists, internists, surgeons, social workers, and psychologists is discussed. The book is planned with two chapters of preparatory material. The first chapter, which is concerned with principles and applications of psychosomatic medicine, gives a short review of the anatomic basis of emotional behavior and discusses three mechanisms of emotion, the evidence supporting emotions as a cause of disorders of function, the evidence that emotions may be one of the causes of lesions, selectivity of reactions, and psychophysiological sequences. The second chapter discusses the physician-patient relationship and its role in therapy. Following this are 21 case reports and conference presentations that cover a wide range of psychosomatic problems.

It is questionable whether the introductory chapters would satisfy the psychiatrist, the student, the general practitioner, or a specialist in any field. The chapter on the physician-patient relationship contains several ideas that seem to be used in an unusual way; for example, on page 38, the authors discuss constitutional factors from the physician's side of the physician-patient relationship and base their discussion on the physician's sex, age, and racial or national background. Although these factors are important, it is questionable whether they are constitutional factors.

Some of the conference discussions are disappointing. It is frequently impossible to detect the goals of the physicians taking part in the discussions. It seems as if one discussant is interested in the psychodynamics of the case, another in using the case material to teach, and a third in contributing generally. In addition, there is so much difference in the psychiatric approaches that one becomes confused.

Although the therapy discussed in the book is designated in the foreword as being psychoanalytically oriented, there is little evidence that this is generally so, in spite of the fact that several psychoanalytic formulations are offered. In many instances, the psychoanalytic approach is tied in by simply explaining that the psychoanalyst would use the word "castration" for something that other approaches would call "mutilation." The following quotation appears on page 201: "Some of the concepts developed by psychoanalytic investigations have appeared 'far-fetched' and even ridiculous to some physicians, in many instances because one cannot see explicit confirmation in the material obtained in a few face-to-face interviews." It would seem pertinent to question whether the approach to psychiatric problems by various disciplines is promoted for the student or the nonpsychiatrically trained physician by these demonstrations of how they work together.

Several patients mentioned in the case histories were presented to the staff. On the basis of the records, the presentations seem to have contributed little to the discussions; however, other psychiatrists have found that the presentation of the patient to the group can be beneficial to both patient and physicians.

In many of the case histories, the therapeutic approach seems to be highlighted by a warm, friendly, accepting physician-patient relationship. The role of therapy for patients whose cases are reported as failures therapeutically but who show remarkably beneficial results in the follow-up will be difficult for the beginner to understand. Although the purpose of this book, the need for discussion of the psychosomatic approach, is laudable, this effort does not, in general, achieve its aim.

The Cost of Sickness and the Price of Health. By C.-E. A. Winslow, Dr.P.H., Consultant in Public Health Administration, World Health Organization, Geneva. World Health Organization Monograph Series, no. 7. Paper. $1.50; 7/6; 6 Sw. francs. Pp. 106. World Health Organization, Palais des nations, Geneva; [Columbia University Press, 2960 Broadway, New York 27], 1951.

As part of a program for improved world health, Dr. Winslow, professor emeritus of public health at Yale University, has prepared this monograph as a basis for discussions on the economic value of preventive medicine. His thesis is that mankind suffers from many grave preventable diseases that not only involve human suffering but also impose a heavy burden on the economic resources of the regions involved. Cited studies indicate that "prevention is not only better than cure, it is also cheaper than cure." A recent study by the United States Committee on the Costs of Medical Care covering 9,000 families over a one year period showed that seven days a year were lost on account of illness, exclusive of institutional cases. It has recently been reported that in 1949 the United States had a total national income of $217,000,000,000 of which $10,600,000,000 (5%) was spent on medical and institutional care of the diseased. Any attempt to translate the statistics of life expectancy and disease prevention into terms of financial value to the community is difficult because of demographic differences of various countries.

There seems to be a high correlation between poverty and disease, or as Dr. Winslow states, "Poverty causes disease and disease creates more poverty in a vicious circle." But the prob-

The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

lem does not end with the elimination of poverty or the creation of a sound financial system. It requires the integration of all the resources of agriculture, industry, economics, and education, with the combined effort aimed at better, more healthful living.

As a consultant to the World Health Organization, the author feels this organization should guide programs and studies in which the more fortunate areas may cooperate with those of less advanced development for the common goal of a healthful, prosperous, and peaceful world. Achievements that have been made in environmental sanitation, control of diseases spread from man to man, promotion of mental health, and promotion of positive health such as maternal and child care and nutrition, are listed and evaluated in areas where such achievement can be more easily measured. Plans, programs, studies, blueprints, outlines, and volumes of good suggestions are, unfortunately, worth very little unless they are financially and socially possible and until they are set in motion, since success is measured by the actual delivery of essential services.

You and Your Aging Parents. By Edith M. Stern and Mable Ross, M.D., Director, Prince Georges County Mental Health Clinic in Maryland. Cloth. $2.75. Pp. 212. A. A. Wyn, Publisher, 23 W. 47th St., New York 19, 1952.

One of the most important dividends of disease control by medical science is the prolongation of lives. Numerically, older citizens are increasing. Accordingly, many problems are confronting the medical profession. Not the least of these is the care of elderly parents. Questions concerning their relationship to their children, living quarters, physical care, and routine living are often the responsibility of their children.

This book discusses, in readable style, over 100 real-life histories that describe situations likely to appear. The book is written particularly for the children. It should be kept in mind that many elderly parents are capable of managing their own affairs; they cannot be classified as problem oldsters; and, as far as possible, they should guide their own destinies.

All too frequently, time brings about diminished resources. These situations are discussed in five sections: (1) the challenge of aging parents, (2) their living apart from their children, (3) their doubling up with other members of the family, (4) bereavements of aging parents, and (5) old age expectancies, safety, and comfort. A number of personal items such as illness and diet are discussed.

In this attractive volume, many families will find helpful suggestions that will enlighten them in their search for adequate answers to vexing problems that arise as their parents grow older. This book gives much detailed information that thousands of families with elderly parents will find of inestimable value.

Anatomy and Physiology for Nurses. By W. Gordon Sears, M.D., M.R.C.P., Physician Superintendent, Mile End Hospital, London. Second edition. Cloth. $2.50. Pp. 395, with 204 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2; Edward Arnold & Co., 41-43 Maddox St., London, W.1, 1951.

The author states that in the preparation of the second edition of this text he has aimed to keep the work as simple as possible without sacrificing the scientific and technical approach to the subject. Then he has attempted to include all facts that are essential for examination purposes and for meeting the requirements of the syllabus laid down by the General Nursing Council of England and Wales for the preliminary state examinations. Thirdly, his aim has been to present sufficient facts to make the subject understandable and interesting. And lastly, facts are included that have a subsequent practical application and serve as basic information for the study of other subjects in the curriculum.

The data on anatomy, designed to meet the requirements of students in nursing schools in Britain, may not, in all instances, be sufficiently detailed to serve as an anatomy text for nursing schools in the United States. The material on physiology is not explained and integrated to the degree that is essential if the subject is to be understood and applied in actual nursing practice. While the author states as his aim the promotion of understanding, interest, and ability to apply, his material seems actually to be directed essentially towards presenting facts with which average examination questions can be answered. This is not an uncommon shortcoming of anatomy and physiology textbooks for nurses. While the nursing curriculum does not allow for an extensive study of physiology, there is an urgent need for intensive study of a few basic physiologic principles that are essential in nursing knowledge and practice. While classroom instruction will contribute considerably to greater understanding and integration, a textbook is not fulfilling its purpose if its material does not at least approximate that which will be covered in the classroom.

This book by an English physician includes 15 chapters, each devoted to a system of the body. The style of presentation is almost in outline form. Under some circumstances, this book may be useful as a text on anatomy. It is doubtful if it can be effective as a text or reference on physiology for student nurses.

Untoward Reactions of Cortisone and ACTH. By Vincent J. Derbes, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University of Louisiana School of Medicine, New Orleans, and Thomas E. Weiss, M.D., Instructor in Medicine, Tulane University of Louisiana School of Medicine. Publication number 131, American Lecture Series, monograph in American Lectures in Internal Medicine. Edited by Roscoe L. Pullen, M.D., Director, Division of Graduate Medicine, Tulane University of Louisiana. Cloth. $2.25. Pp. 77. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, 1951.

The authors have been able to crowd a surprising amount of information into this short monograph, which is succinctly worded and excellently documented. The treatise first considers the physiological effects of corticotropin and cortisone and then illustrates how their physiological effects may be exaggerated into untoward reactions by treatment. The authors emphasize that treatment dosage, except in deficiency states, constitutes an unphysiological quantity of hormone, and outline the effects that may occur in various anatomic systems. The salient factors of interest are given in outline form at the head of each chapter; they are then more fully developed in the text. This handling of textual material is a definite aid to study and review. With the exception of the physiological considerations, the ideas concur with present day thought. This book is recommended as an excellent teaching and review text for medical students and physicians.

A Practical Handbook of Midwifery and Gynæcology for Students and Practitioners. By W. F. T. Haultain, O.B.E., M.C., B.A., Hon. Consulting Obstetrician and Gynæcologist, Royal Infirmary, Edinburgh, and Clifford Kennedy, M.B., Ch.B., F.R.C.S.Ed., Assistant Obstetrician and Gynæcologist, Royal Infirmary, Edinburgh. Including Section on The Management of the Infant and Neo-Natal Conditions. By J. L. Henderson, M.D., F.R.C.P.Ed., Professor of Child Health, St. Andrews' University, Dundee. Fourth edition. Cloth. $6. Pp. 412, with 48 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2; E. & S. Livingstone, 16 and 17 Teviot Place, Edinburgh 1, 1952.

This edition of this practical handbook of obstetrics and gynecology has been revised extensively, and new material has been added. The chapter on newborn and infant feeding has been brought up-to-date by Dr. J. L. Henderson, professor of child health at St. Andrews' University. A new section on the Rh factor has been written, and the section on venereal diseases has been revised.

The authors discuss modern teaching in this specialty. All the subjects are treated in a concise manner, many in outline form, devoid of nonessential details. Thus, the student or practitioner, for whom this book is intended, can easily obtain essential clinical data and ideas on appropriate therapy. A few carefully chosen illustrations amplify the text.

Although one finds reference to some practices that have become obsolete in the United States, such as uterine douching for hemorrhage, the obstetric and gynecologic teaching is sound and in the best Edinburgh tradition. This handy synopsis can be heartily recommended to students and general practitioners.

Human Biochemistry. By Israel S. Kleiner, Ph.D., Professor of Biochemistry and Director of Department of Biochemistry, New York Medical College, New York. Third edition. Cloth. $7. Pp. 695, with 88 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1951.

In this edition, many chapters have been revised considerably, particularly those sections concerned with mineral metabolism and water balance, respiration and acid-base balance, blood coagulation, and vitamin A function. New material has been added, but, because of restrictions on the size of the book, it was necessary to give only limited space to the discussions.

The topics covered include carbohydrates, lipids, proteins and their metabolism, tissues, milk, blood, urine, enzymes, digestion, vitamins, foods, physiological oxidations, mineral metabolism and water balance, chemistry of respiration and acid-base balance, energy metabolism, hormones, chemical structure in relation to biologic phenomena, and recent clinical applications. The last-mentioned chapter includes brief sections on liver function tests, kidney function tests, dental caries, biochemistry of inflammation, biochemistry of tumors, acid phosphatase and the prostate gland, antibiotics and sulfa drugs, radioactive isotopes, mucolytic enzymes, cortisone and corticotropin (ACTH), and pyrogens.

Each chapter has general and special references that include some of the literature through 1950. The appendix includes a table of standard buffer solutions, one for the composition of foods and another for the sodium and potassium content of foods.

Living in Balance. By Frank S. Caprio, M.D. Cloth. $3.75. Pp. 246. Arundel Press, Inc., P. O. Box 2606, Washington 13, D. C., 1951.

Dr. Caprio, in the preface to his book, states that "one of its purposes is to show how nervous breakdowns can be prevented . . . to teach the reader to achieve better living through better thinking." In a good measure he has succeeded. His style and arrangement is particularly designed to capture the interest of a large group of persons who, knowing little or nothing of the workings of the human mind, wish to learn how mental and nervous illness begins and what can be done about it. Some of Dr. Caprio's concepts and formulations are open to argument, but, generally, he has lucidly and simply discussed, in everyday language, the basic principles that reflect the attitude of present-day psychiatry. The chapter on self-analysis through dream interpretation might well have been omitted.

The chapters on marital situations, sex, fear, alcoholism, and neurotic reactions are written in a manner that will stimulate interest in persons who happen to need advice and guidance. The busy medical practitioner could well recommend this work to a large group of patients who come to him with perplexing problems of everyday living.

Textbook of Biochemistry. By Edward Staunton West, Ph.D., Professor of Biochemistry, University of Oregon Medical School, Portland, and Wilbert R. Todd, Ph.D., Associate Professor of Biochemistry, University of Oregon Medical School. Cloth. $12. Pp. 1345, with 80 illustrations. The Macmillan Company, 60 Fifth Ave., New York 11, 1951.

This book includes an excellent discussion of the principles of physical and organic chemistry, a feature that is often inadequately discussed in biochemistry texts. These principles are introduced in chapters on gases and solutions, electrolytic dissociation and the mass law, acids, bases, and buffers, osmotic pressure, the colloidal state and membrane phenomena, lipids, carbohydrates, monosaccharides, compound sugars, proteins, nucleoproteins, and nucleic acids. These sections comprise about 30% of the book. Correlation between facts and the underlying principles are repeatedly stressed throughout the book for pedagogic reasons.

The major portion of the text is comprehensive and detailed, with chapters on composition of tissues, enzymes, digestion, absorption, detoxication, bloods and body fluids, respiration, acid-base balance, electrolyte and water balance, energy metabolism, vitamins, biologic oxidation-reduction, intermediary metabolism, organic phosphates in metabolism, chemical energetics, lipid, carbohydrate, and protein metabolism, nutritional aspects of proteins, amino acids, lipids, and carbohydrates, metabolism of inorganic elements, foods, urine formation and composition, hormones, and antimetabolic agents.

There are many formulas, charts, and tables. The numerous tables of composition and values of biologic data compiled in one volume enhances its value as a ready reference work.

The material is clearly discussed, and both general and special references are included. This book is highly recommended to the physician to bring him up-to-date on the status of biochemistry in medicine and to the student who will be able to better appreciate the relationship between apparently isolated biochemical phenomena and general chemical and physical principles.

The Child in Health and Disease: A Textbook for Students and Practitioners of Medicine. By Clifford G. Grulee, M.D., Rush Professor of Pediatrics, University of Illinois, Chicago, and R. Cannon Eley, M.D., Assistant Clinical Professor of Pediatrics, Children's Hospital, Children's Medical Center, Harvard University Medical School, Boston. Second edition. Cloth. $15. Pp. 1255, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

This text on pediatrics will be useful to students and general practitioners of medicine. In the preface, the authors give two reasons for sponsoring the second edition: first, medicine is moving so rapidly that the print is scarcely dry before there is something new on the subject; second, new subjects have been incorporated that were not included in the first edition. These subjects, rare in textbooks on pediatrics, include medical supervision in summer camps, cardiovascular surgery, viral hepatitis, erythroblastosis fetalis, and pancreatic fibrosis. The material is printed in two columns on each page. The book is easy to read, and each chapter contains a bibliography. Dr. Grulee's experience as a teacher of pediatrics, as editor of the *American Journal of Diseases of Children* for many years, and his official position with the American Academy of Pediatrics make him particularly well qualified to select the proper authors for the various chapters. A book of this type, which is so up-to-date, should perhaps be made into a loosely bound volume, so that newer aspects and more recent chapters can be added from time to time. This text is an excellent addition to the library of the pediatrician, general practitioner, or student of pediatrics.

Shock Treatments, Psychosurgery and Other Somatic Treatments in Psychiatry. By Lothar B. Kalinowsky, M.D., Research Associate in Psychiatry, College of Physicians and Surgeons, Columbia University, New York, and Paul H. Hoch, M.D., Principal Research Scientist (Psychiatry), New York State Psychiatric Institute and Hospital, New York. Foreword by Nolan D. C. Lewis, M.D., Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, New York. Second edition. Cloth. $8.75. Pp. 396. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1952.

This is an enlarged edition of the only authentic textbook on the place of the physical therapy in psychiatry. A large section on psychosurgery is included in the edition as well as a chapter on theoretical considerations. The extensive research into sources of data, which the authors have critically integrated with their personal experiences, is indicated by the 52 pages of bibliography. The book is well written and the subject matter demarcated to enable easy reference to various aspects of the subject. For psychiatrists employing physical therapy, this work should be a great help.

A Bio-Bibliography of Edward Jenner, 1749-1823. By W. R. LeFanu. Limited numbered edition. Cloth. $16. Pp. 176, with 29 plates. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C.2; 2083 Guy St., Montreal, 1951.

This volume consists of a catalogue of the writings of Edward Jenner, the discoverer of vaccination, together with a brief bibliographic sketch and numerous excellent photographic reproductions of original manuscripts and title pages. The book will be of interest largely to book collectors and librarians; however, the general reader will find that it contains much of interest, especially if he is unaware of the wide variety of investigations undertaken by this 18th century scientist, many in collaboration with his teacher and friend John Hunter.

QUERIES AND MINOR NOTES

LABORATORY FACILITIES IN RURAL AREA

To the Editor:—*My clinic in a rural area is 38 miles from the nearest clinical laboratory. We make our own electrocardiograms, x-ray examinations, basal metabolic rate studies, routine urinalyses, blood cell counts, and sedimentation rate studies. It is impossible to obtain a registered laboratory technician; therefore, to obtain chemical analyses, we are obliged either to mail the blood or to send it by bus to the laboratory mentioned, and often the blood is unsuitable for examination by the time it reaches its destination. Furthermore, the accuracy of tests on mailed blood specimens can be challenged. Are there simple, accurate methods of chemical analysis that can be performed by untrained personnel? Is a photoelectric colorimeter simple enough for use by untrained personnel? In mailing the specimens, what preservative should be used? How long will blood keep under mailing conditions? Kindly discuss this in relation to such determinations as nonprotein nitrogen, urea nitrogen, blood sugar, chloride, sodium, cholesterol, and protein levels, and liver function tests. I believe this to be an acute problem in rural practice, especially since we younger men are attempting to establish the same high standards of medical care that prevail in larger cities.*

J. J. Kirschenfeld, M.D., Fort Deposit, Ala.

Answer.—Whether it is logical to establish a routine blood chemistry laboratory in a rural clinic when it is impossible to obtain a registered laboratory technician is not a simple question; however, if an adequate clinical laboratory is available within 38 miles, it would appear that it would not be logical. There are many advantages that rural areas do not have, including brain surgeons, laboratories for cardiac catheterization, and general clinical laboratories. There are no simple, accurate, and foolproof methods for chemical analyses, and chemical analyses cannot be performed by untrained office personnel. Photoelectric colorimeters are highly technical instruments and require constant attention by someone skilled in their use, and highly trained personnel are needed to calibrate them. If the clinical laboratory referred to is within 38 miles of the rural clinic, it would appear that a satisfactory arrangement could be made with the laboratory for examining and reporting on specimens. This presupposes that the laboratory is competent. There are anticoagulants that have been described as being satisfactory for shipping specimens by mail. They vary with the test to be performed and the method used. Sodium fluoride and thymol will preserve specimens for sugar determinations and many other tests but cannot be used for urea. Sodium oxalate can be used when urea is to be tested.

STIMULATION OF GROWTH

To the Editor:—*A 15-year-old boy is only 5 ft. 1 in. (154.9 cm.) tall. His physical development is entirely normal, except for his height, which is partly a family characteristic. Would hormone therapy help his growth?*

N. B. Livingston Jr., M.D., Mohall, N. D.

Answer.—The patient should be carefully studied from a general medical and endocrinological point of view. Roentgenograms should be taken of the bones of the elbow, hands, and knees to see whether epiphyseal closure has occurred and to estimate the growth potential remaining in the skeleton. If the epiphyses are closed, future growth is impossible. If they are open, the degree of potential growth can be estimated by careful study. If the patient has hypothyroidism, the administration of desiccated thyroid will stimulate growth. If his basal metabolism is within normal limits and he is maturing sexually at a satisfactory rate, no form of therapy will be effective. If the patient is sexually immature, growth of the skeleton can be stimulated by the administration of chorionic gonadotropin or androgen. Androgen is not a substitute for the thyroid hormone or for the growth hormone of the pituitary, without which the skeleton cannot attain normal length. Roentgenograms of the sella turcica should be made to exclude the presence of a pituitary tumor. The growth hormone of the pituitary is not very effective in stimulating growth in man.

LOSS OF HAND FUNCTION

To the Editor:—*Please give an opinion on the percentage loss of function of a hand in which there remains a good functioning thumb, two-thirds of the middle finger, slightly over one-half the ring finger, and a little over one-half the small finger. The patient closes his hand with some difficulty because of residual swelling in the palm and in the amputation stumps.*

M.D., New York.

Answer.—Since there is no uniform system of rating disability in all states in this country, it is difficult to give an opinion on the percentage loss of function of this hand. Although it may be possible to ascribe a certain percentage of disability based on the loss of part or all of certain digits, a major factor in considering the percentage loss of function should be the particular loss of function that has resulted in this case. Before establishing a permanent disability rating, it should be determined whether further improvement in the usefulness of the hand can be obtained by the use of rehabilitative procedures, including physical therapy and occupational therapy. The patient's occupation should also be considered in determining the amount of final disability. Assistance in determining the percentage loss of function may need to be obtained by reference to tables of disability acceptable to the various parties having an interest in this particular case. The complexity of the problem of determining the percentage loss of function of a hand is apparent in an excellent discussion of this subject that appears in the book "Accidental Injuries" by H. H. Kessler (ed. 2, Philadelphia, Lea and Febiger, 1941).

ELECTRIC SHOCK TREATMENTS

To the Editor:—*Some of my patients with melancholia were given electric shock treatments years ago, but I was discouraged by the violent reactions produced and the uncertain results. Do the later type machines produce the violent convulsions produced by the older types, and do they produce better results?* *W. B. Chapman, M.D., Joplin, Mo.*

Answer.—Electric shock therapy involves the application of electric currents to the head. These currents usually vary from 300 to 1,200 ma., produced by voltages of from 70 to 150 volts, and current passage times of 0.1 to 0.5 seconds are used. The purpose of the application of these currents is to produce a convulsive seizure. The dose required for production of the convulsive seizure varies from patient to patient and must be determined by the person applying the treatment. The use of an electrical device in shock therapy is advantageous in that application is simple and it is possible to induce either minor or major seizures. Modifications in the older type machines have been made, but the machines still produce a convulsive seizure.

Some use has been made of tubocurarine chloride to reduce the contractile power of the skeletal muscle in conjunction with electric shock therapy. For shock treatment as used in psychiatry, New and Nonofficial Remedies (Chicago, American Medical Association, 1952, p. 431) gives the usual dose of tubocurarine chloride as 3 mg. (20 units) for each 40 lb. (18.1 kg.) of body weight. Usually, for greater safety, a smaller dose is used initially.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

ASYMPTOMATIC NEUROSYPHILIS

To the Editor:—*A woman, aged 45, is symptom-free from latent syphilis. Her weight has not changed in 10 years. She gives a history of latent acquired syphilis of 22 years duration. In 1950, her husband developed cerebral spinal syphilis with paresis. At that time she sought treatment and was given 600,000 units of penicillin daily for 15 days. On Jan. 17, 1952, a blood serum test was strongly positive (4+) for syphilis. The results of a spinal fluid examination were as follows: quantitative reaction to Wassermann test, 444; 1 white cell per cubic millimeter; the globulin level was normal, the total protein content being 19 mg. per 100 cc.; and the colloidal gold test reaction was 1122100000. What treatment is indicated for this patient? Should treatment with a saturated solution of potassium iodide be continued?*

M.D., Pennsylvania.

Answer.—If the patient described has not yet been examined by a skilled neuropsychiatrist, such a consultation should be promptly requested. If the results of his examination are normal, the patient may be considered as having asymptomatic neurosyphilis. If the latter proves to be the correct diagnosis, the patient is not in need of further treatment. The spinal fluid apparently was not examined before the patient received treatment. On examination 8 months after the administration of 9 million units of penicillin, the spinal fluid is "inactive" in the sense that the cell count and protein content are normal. The normality of these two tests indicates that whatever inflammatory component of the asymptomatic neurosyphilis may have been present when treatment was started has now been adequately dealt with. There is a 90 to 95% certainty that this result will be permanent. Nothing is gained by the administration of potassium iodide, arsenic or bismuth, or, for the time being at any rate, additional penicillin therapy or fever therapy.

The patient should be followed from this point with repeated physical (especially neuropsychiatric) examinations and with recheck examinations of the blood serum and the spinal fluid at intervals of every 6 months for the next 3 years, at yearly intervals thereafter for another 3 years, and at somewhat longer intervals after that. Indications for retreatment will be the appearance of clinical signs or symptoms of neurosyphilis of any type or the reappearance in the spinal fluid of an increased cell count and/or protein content. The persistence of a positive complement fixation test and/or flocculation test in the blood and spinal fluid may be ignored as long as the patient's physical condition and the cell count and protein content of the spinal fluid remain normal.

UNDESCENDED TESTES IN YOUNG BOY

To the Editor:—*What is the consensus regarding treatment of a 3-year-old boy with bilateral undescended testicles? The boy is otherwise well developed, but the testicles cannot be palpated either in the scrotum or in the canals. The penis is extremely small and was noted as being very small at birth. The pregnancy and delivery were uneventful. Other siblings are normal, as are the parents.*

M. E. Friedman, M.D., New Buffalo, Mich.

Answer.—The following point of view is the one most generally accepted concerning the treatment of undescended testes: 1. Accurate diagnosis is important. The patient should be examined at least twice in both the upright and recumbent positions to ascertain the exact location of the testis. 2. The earlier the testis is brought into the scrotum the better its function in later life. The testis cannot function normally except in the environment of the scrotum. The longer it remains at some level above the scrotum, the greater the likelihood of permanent damage. 3. Glandular treatment should be instituted as soon as it is practical to carry out operative procedures so that these may be used if glandular therapy is not effective. This means that treatment should be started by about the age of 3 years. 4. The material of choice is chorionic gonadotropin. It should be given in a dose of 500 I. U. by intramuscular injection 3 times a week. In patients with bilateral undescended testes, chorionic gonadotropin may be ineffective. Under these circumstances, testosterone propionate should be given in a dose of 25 mg. 3 times a week by intramuscular injection. 5. If glandular therapy is effective, descent will usually occur within eight weeks. If the treatment is ineffective, operative procedures should be carried out at once by some one specially skilled in this field. Great care must be taken to preserve the blood supply of the testis. Glandular therapy should be continued until the time of operation. 6. Only a small amount of genital growth should be induced. This means that chorionic gonadotropin and testosterone propionate should not be continued for a long period of time in a young boy.

FERTILITY IN MEN

To the Editor:—*What effect, if any, have the following on fertility in men: (a) inhalation of carbon tetrachloride, (b) high altitude flying, (c) inhalation of fumes of the galvanizing process, (d) exposure to radar waves, as experienced by naval personnel who are in fairly constant contact with them, and (e) infectious hepatitis?*

Norman L. Wilson, M.D., Quincy, Mass.

Answer.—(*a*) Inhalation of carbon tetrachloride does not cause male sterility. The liver detoxicates this chemical. (*b*) High altitude flying over long periods of time has not been proved to cause male sterility. Modern airplane cabins have both pressure and oxygen control for human safety. (*c*) In the galvanizing process, iron is coated with tin and is then immersed in a zinc bath. Physiological damage from exposure to this process would be the same as occurs in lead or zinc poisoning. Progressive anemia may occur and may result in temporary or permanent sterility. (*d*) Exposure to radar waves does not cause sterility. Radar waves are high frequency electromagnetic radiation and may have the same frequency as short-wave or ultrashort-wave radio waves. They do not produce ionization within tissues and cannot cause sterility. The alpha, beta, and gamma rays generated by radioactive substances, such as radium, or by x-ray apparatus are the three types of rays usually considered in the problem of sterility. The gamma rays are those that produce sterility; the beta rays, it is believed, probably do not produce sterility; the alpha rays cannot produce sterility. (*e*) In infectious hepatitis as a primary infection of the liver, secondary sites of infection may develop as a result of invasion by the infecting organism, after its transmission through the blood stream. Orchitis may result, with unilateral or bilateral sterility, depending on the severity of the attack and the extent of involvement (one or both testicles). Mechanical blocking of the vas deferens by invading organisms, such as filariae and amebas will prevent egress of spermatozoa from the vas deferens, causing male sterility. High body temperatures sustained over long periods of time can destroy the ability of the testes to manufacture spermatozoa.

DIATHERMY IN REGION OF METALLIC IMPLANTS

To the Editor:—*A patient with several silver wires in her fractured patella needs short wave diathermy for her arthritic knee. Is it dangerous to apply diathermy to bones with silver wires in them? Is there a type of diathermy (for instance, diathermy by Microtherm®) that can be applied with safety?*

M.D., New York.

Answer.—Both short wave and microwave diathermy, which are effective in heating human tissues, are even more effective in the heating of metals. For this reason, it is generally felt that in any condition in which metallic implants are present near the area or in the area to be treated, short wave and microwave diathermy are contraindicated. Metallic substances, such as bullets, screws, bands, and wires in tissues may be excessively heated if diathermy is applied. It is known that, in many instances, damage has not occurred, but there is a potential danger, both actual and theoretical, which makes it advisable to heat these areas by means other than medical diathermy.

REFERENCE

Lion, K. S.: The Effect of the Presence of Metals in Tissues Subjected to Diathermy Treatment, Arch. Phys. Med. **28**: 345-347 (June) 1947.

PENICILLIN INJECTIONS

To the Editor:—*In* The Journal, *June 28, 1952 (page 906), the answer to the query about penicillin injections contains a serious error. It suggests the use of "two injections a day of 300,000 to 600,000 units of crystalline penicillin G or K." A number of years ago it was conclusively shown that penicillin K was relatively ineffective in almost all infectious diseases. It is not obtainable commercially, and all penicillin manufacturers make every effort to remove penicillin K from their products. The only penicillins now commercially available are penicillin G and penicillin O in the form of one or another of their salts. The answer is further at fault in that it makes no distinction between repository preparations of penicillin G and aqueous solutions of crystalline penicillin.*

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Baltimore 1.

FLUORIDE BY MOUTH DURING PREGNANCY

To the Editor:—*In answering the question of whether fluoride given to the mother by mouth during pregnancy will cause the baby to have better teeth in life, it is stated that there is no evidence that fluoride taken by the mother during pregnancy will cause a baby to have better permanent teeth* (J. A. M. A. *March 1, 1952).*

In the April, 1951, Journal of Dental Medicine, *Dr. Reuben Feltman of Passaic, N. J., writes "Since 1948, 309 children have been born to mothers who have ingested tablets containing 2 to 4 mgms. of Calcium fluoride daily. Some of the children who were born from these mothers have been examined. The results to date are most heartening,—the numbers are too small and the ages too young to be of importance at this stage of the investigation.*

"This much can be reported, the caries rate in three year olds in this area is two decayed teeth. Caries has been found in only one child. The enamel has the appearance of the inside of an oyster shell highly polished and pearly."

The following quotation is from "Industrial Fluorosis: A Study of the Hazard to Man and Animals Near Fort William, Scotland" (Medical Research Council, Memorandum no. 22, London, His Majesty's Stationery Office):

"Evans Phillips and Hart (1938) suggested that fluorine is transferred through the placenta of the cow to the foetus. Velu (1936) held that fluorine in young animals born of mothers exposed to fluorine must have passed to the foetus. Knouff (1936) confirmed the passage of fluorine through the placenta of bitches."

Ample evidence has been compiled from the literature to lend feasibility to the theory that fluorine ingested during pregnancy and the formative years of tooth development will cause a reduction in the incidence of dental caries. There is a maternal transference of fluorine, which makes both the deciduous and permanent teeth less subject to caries if the child continues to get the optimum daily dose regularly.

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To the Editor:—*A question concerning the effect of fluoride given by mouth during pregnancy was answered in your column in* The Journal *of March 1, 1952, with the statement that "the tooth buds of the permanent teeth are not even formed at the time of birth [so] it is difficult to see how fluoride can affect the baby's future teeth in utero."*

According to J. A. Salzmann (Principles of Orthodontics, Philadelphia, J. B. Lippincott Company, 1943, p. 182) epithelial buds are present for the permanent incisors, cuspids, bicuspids, and first molars at the time of birth, and differentation of the tooth germ has so far advanced that calcified tissue is found in the germ of the maxillary and mandibular first permanent molars. The permanent mandibular first incisor also shows calcification. The tooth germ of the permanent maxillary first incisor and the permanent mandibular second incisor have reached a high degree of development. The precursors of the other teeth listed above are described as small undifferentiated buds at this stage.

It would seem, therefore, that the failure of ingested fluoride to affect the baby's teeth in utero must depend upon some mechanism other than the lack of permanent tooth buds in the fetus. Such failure, it is not inconceivable, may even be apparent rather than real and due to difficulties in assembling and evaluating clinical material.

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PAINFUL FEET

To the Editor:—*I would like to add the following aids that I have found valuable in the treatment of metatarsalgia to that described in* The Journal *March 8, 1952 (p. 877):*

1. The use of carpeting with foam rubber underpads to provide a soft walking surface in the home or office. 2. The addition of an extra leather sole to the shoe. This helps tremendously to give a cushioned effect to the sole of the shoe. 3. Application of metatarsal bars to the shoe. I have found it best to make and apply these myself.

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PROGRESSIVE MYOPIA IN A CHILD

To the Editor:—*In the query concerning progressive myopia in a child in* The Journal *March 29, 1952 (page 1165), a statement was made that "The amount of correction of myopia has no effect on the progress of the refractive error." I agree that in some young patients who abuse their eyes, myopia cannot be checked even with the strongest glasses; however, in most cases the progress of myopia can be decreased by the use of full correction eyeglasses. This favorable outcome is significant socially, particularly for girls. If the myopia can be checked at the strength of three diopters, attendance at formal functions later in life will be possible without eyeglasses.*

I disagree with the philosophy that "There need be no insistence on the wearing of the glass unless clear vision is preferred by the patient." This erroneous concept is contrary to the concepts of modern preventive ophthalmology and may explain why some physicians do not refer young myopic patients for refraction until complaints of poor vision are recorded by the school authorities. The progress of myopia is accelerated when the indifference suggested in the reply is practiced. Normal or 20/20 vision must be demanded by all practitioners and not left to the whims of children or their parents.

Teachers in the field of eye muscle dysfunctions know that in young myopic patients with accommodative exophoria who fail to wear eyeglasses constantly the muscle imbalance may be aggravated and divergent strabismus may develop. In a series of cases previously reported (Smith, J. W.: The Problem of Strabismus in Childhood, with Especial Reference to Convergent Strabismus in Infancy and Early Childhood, Am. J. Ophth. **31:***85 [Jan.] 1948), 10% of patients in early stages of divergence were restored to orthophoria by continually wearing eyeglasses to correct their myopia.*

It is regrettable that authorities are not in agreement regarding the treatment of myopia. In my experience, extending over thirty years, early and full correction and insistence on the constant wearing of the glasses during the school years is the regimen that pays dividends in good eye health. This plan insures the minimum of progression and in many cases actually arrests the myopia.

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